"ASSESSMENT OF CORRECTED Q-T INTERVAL DURING HYPOGLYCEMIC EPISODES IN DIABETIC PATIENTS"

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M.D GENERAL MEDICINE

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CHENNAI, TAMILNADU, INDIA

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled**"ASSESSMENT OF CORRECTED Q-T INTERVAL DURING HYPOGLYCEMIC EPISODES IN DIABETIC PATIENTS"** is the bonafide work of **Dr.K.Ramkumar,**in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015**

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DECLARATION

I, Dr.K.Ramkumar, solemnly declare that this dissertation titled**"ASSESSMENT OF CORRECTED Q-T INTERVAL DURING HYPOGLYCEMIC EPISODES IN DIABETIC PATIENTS"** is a bonafide record of work done by at the Department Of General Medicine , Government Rajaji Hospital, Madurai, under the guidance of **Dr. S.VADIVELMURUGAN ,M.D,** Professor , Department of General Medicine , Madurai Medical college , Madurai

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **April 2015.**

Place: Madurai

Date: **Dr.K.Ramkumar.**

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ABSTRACT

INTRODUCTION:

In an adult human, hypoglycaemia causes physiological responses in the form of autonomic activation, principally of the Sympatho-adrenal system, and results in secretion of adrenaline and end-organ stimulation. Blood supply is increased to the myocardium, the brain, the splanchnic circulation.

The following hemodynamic changes will occur in our body such as elevation of heart rate and peripheral systolic Bp, a fall in central blood pressure, decrease in peripheral arterial resistance, and increased myocardial contractility, stroke volume, and cardiac output due to hypoglycaemia. The workload of the heart is temporarily increased. Patients with normal cardiovascular system can tolerate this transient cardiac stress. But patients who are all having DM and other risk factors cannot tolerate this transient myocardial stress and develop complications like arrhythmias and sudden cardiac cardiac death.

In non-diabetic individuals arteries will be more elastic during hypoglycaemic state with decline in arterial wall stiff ness. But patients with diabetes, arterial wall stiffness is greater and arteries will become less elastic during hypoglycaemia. These changes cause hemodynamic abnormality like lesser

fall in central aortic pressure. This progressive stiffness of arterial wall reduces myocardial perfusion and promotes myocardial ischemia.

Hypoglycaemia causes ST Segment changes and lengthening of Q-T interval and cardiac repolarisation abnormalities. This causes in coordinated contraction of cardiac muscles. Profuse release of catecholamine causes hypokalaemia. All these changes causes cardiac rhythm abnormality such as ventricular tachycardia, atrial fibrillation.

The increased sympathetic activity and concurrent secretion of hormones like endothelin causes vasoconstriction abnormalities in viscosity.

Viscosity - Increased erythrocyte concentration.

Coagulation-platelet activation, raise in factor VIII, von willebrand factor

Endothelial dysfunction-increase in CRP.

These changes promote intravascular coagulation and thrombosis.

AIMS AND OBJECTIVES OF THE STUDY:

To assess the corrected Q-T interval during hypoglycemic episodes in diabetic patients with respect to their baseline characteristics- sex, Type of Diabetes, duration of Diabetes.

MATERIALS AND METHODS

SELECTION OF STUDY SUBJECTS:

This study is to be conducted in diabetic patients who are all admitted in medical ward with symptoms of severe hypoglycemia at Govt. Rajaji Hospital, Madurai. Severe hypoglycaemia was defined in this study, as the condition requiring active medical intervention such as carbohydrate administration when plasma sugar level was <60 mg/dl. I categorise the patients into 4 groups according to their blood sugar levels. Cat I—60-50 mg/dl, Cat II—40-50 mg/dl,

Cat III—30-40mg/dl, Cat IV--<30 mg/dl

STUDY POPULATION:

100 cases

RESULTS:

Out of 100 cases 75 patients developed Q-T c prolongation. 24 patients from Cat-1& 2 and 51 patients from Cat-3&4 are developed Q-T prolongation in our study with significant p value of .048. In our study 448 ms was a mean Q-T interval in Cat I. As the blood sugar level decreases Q-T prolongation increases up to 519 ms in Cat IV. P value-0.001

In our study 4 patients in Category -III ,6 patients in Category-IV developed arrhythmias with statistically significant P value of 0.010. Chi square value-6.67

. In our study 5 patients were died due to arrhythmias in Category -IV and 1 patient died in Category- III. There were no deaths observed in Category I&II with statistically significant P value of 0.047.

CONCLUSION

From our study we conclude, that

Incidence of QTc prolongation is more with severe hypoglycemia. Q-T c interval more than 500millisecond causes Arrhythmia, thereby causing sudden cardiac death. Repolarization abnormality is the most common cause of arrhythmia in severe hypoglycemia (1). Deaths due to severe hypoglycemia are most common in type 2 Diabetes Mellitus patients. Duration of diabetes mellitus is also a risk factor for developing arrhythmia and sudden cardiac death (19)

KEY WORDS: Q-T prolongation, Repolarization abnormalities, Arrhythmias, Hypoglycemia

INTRODUCTION

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AIMS AND OBJECTIVES

The study was done

1) To assess the corrected Q-T interval during hypoglycemic episodes in diabetic patients with respect to their baseline characteristics- sex, Type of Diabetes, duration of Diabetes.

DEFINITION DIABETES MELLITUS:

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia associate with altered carbohydrates, Fat and protein metabolism due to absolute or relative deficiency of insulin secretion and or action.

DEFINITION OF HYPOGLYCEMIA:

AMERICAN DIABETES ASSOCIATION group on hypoglycemia in diabetes as "all episodes of abnormally low plasma sugar concentration that expose the individual to potential harm".

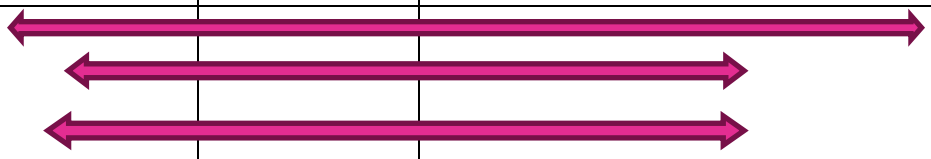
DEFINITION OF HYPOGLYCEMIA IN OUR STUDY:

Hypoglycaemia was defined in this study, as the condition requiring active medical intervention such as carbohydrate administration when plasma glucose level was <60 mg/dl.

CLASSIFICATION OF DIABETES -AMERICAN DIABETES ASSOCIATION

Types of diabetes mellitus **(Etiologic classification of diabetes mellitus)**
Type1: Beta cell destruction usually leading to absolute insulin deficiency a)autoimmune b)idiopathic ***type 2:*** a) primary defect - insulin resistance b) primary defect - insulin secretion ***other specific types of diabetes:*** a) Genetic defects of beta cell dysfunction, e.g. MODY 1 to 6 b) Genetic defects in insulin action, e.g. type A insulin resistance c) Diseases of exocrine pancreas, e.g. fibro calculus pancreatopathy d) Endocrinopthies, e.g. acromegaly, cushings etc., e) Drugs or chemical – induced, e.g. glucocorticoids f) Infections, e.g., congenital rubella g) Uncommon forms of immune-mediated diabetes, e.g. Stiff Man Syndrome h) Other genetic syndromes ***GESTATIONAL DIABETES***

STAGES OF DIABETES:

Stages	**Normo glycaemia**	**Hyperglycemia**	
Types	Normal glucose regulation	Impaired glucose tolerance Or Impaired fasting glucose	**Diabetes mellitus** Not Insulin requiring Insulin requiring For control Insulin requiring for survival
Type 1* Type 2 Other specific types**			
Gestational Diabetes			

Disorders of glycaemia; Etiologic types and stages

TYPES OF DIABETES MELLITUS

Type I DM:

Onset – childhood, adolescence, but can occurs at any age.

Auto immune destruction of β cells

IA – auto antibodies against islet cells, GAD, IA-2, IA-2B, insulin auto antibodies. They are more prone to develop following diseases,

Pernicious Anemia.

Addison's disease

Grave's disease,

Vitiligo,

Thyroiditis,

IB – idiopathic

- Type 1 DM associated with HCA-B8-DR3-and/orDR4.Absent or poor response of glucose stimulated C-peptide levels are diagnostic of type-I diabetes.

TYPE 2:

-Onset -Middle age or after 40 yrs

-Here the basic Pathology is a combination of impaired β cell function, with marked increased in Peripheral Insulin resistance at receptor with raised liver glucose output production.

Coma is rare in type 2 DM, but which may result from hyperglycemia and hyper osmolality

Other specific type (secondary diabetes):

a) Genetic defect of β cell function:

-onset of type-2 diabetes below 25yrs of age classified as MODY

-Inherited through autosomal dominant gene

-They do not have ICA antibodies and are not HLA-DR3 heterozygote

-Glucokinase deficiency is a marker of MODY.

-They are less prone to develop micro and macro vascular complications

-Usually they don't need insulin for diabetic control for varying period from the time of diagnosis

b) Genetic defects in Insulin action e.g.: (type A insulin resistance)

It is associated with Congenital or Acquired Syndromes, like Leprechaunism, lipoatrophy, Acanthosis Nigricans.

DISEASES OF EXOCRINE PANCREAS:

Malnutrition related DM is a type of Diabetes, which is restricted to tropical countries

DIAGNOSTIC CRITERIA OF MRDM:

1) Age of onset <30 yrs.
2) BMI < 19
3) People living in tropics
4) Variable exocrine pancreatic deficiency
5) Requiring high doses of insulin
6) Lack of proneness to ketosis in the absence of stressful situation.

There are 2sub types:

1) Fibro calculus Pancreatic Diabetes
2) Protein Deficient Diabetes Mellitus

Etiology of FCPO*:*

-Incidence is around <1% of Indian population

-Dietary toxins, genetic susceptibility and malnutrition are the causes of FCPO

Classical triad FCPO:

1) Diabetes
2) Recurrent abdominal pain.
3) Pancreatic Calculi

PDDM:

-This condition usually affect malnourished young patients.

-Wasting and stunting are the clinical indicators of malnutrition.

-Pancreatic calcification is not seen in that group.

Endocrinopathies:

-DM may be associated pituitary, adrenal, thyroid glands and gonads dysfunction. Overt diabetes mellitus can occur in acromegalics, diabetes occurring in a Cushing's disease resolves with effective treatment. Schmidt's syndrome is an autosomal recessive condition that usually associates with type1 DM, thyroiditis and failure of adrenal glands.

Drugs or chemical induced:

1) Glucocorticoids
2) ACTH

3) Thiazide diuretics

4) Phenytoin

5) Pentamidine

6) Vacor

Other genetic syndromes:

1) Down's syndrome

2) Turner's syndrome

3) Kleinfelter syndrome

4) Alstroms

5) Lawrence moon biedel

6) Prader willi syndrome

7) Dystrophia myotonica

4. Gestational diabetes mellitus:

It is defined as glucose intolerance in pregnant individual.

In a postpartum period they may revert back to normal or continue to have impaired glucose tolerance or may become frank diabetes.

Fetus of diabetic mother have many diabetic related complications like hypoglycemia, hyper bilirubinemia, hypocalcaemia, macrosomia in the early neonatal period.

Baby born to diabetic mother may prone to develop diabetes in the later part of life

Impaired glucose tolerance:

- It represents transient stage between normal glucose tolerance and type 2 DM

- 2 HR PG 140-199mg/dl

Impaired fasting glucose:

- Stage of impaired glucose homeostasis

- FBS = 100 – 125 mg/dl

- 2HR PG = < 140 mg/dl

Combined glucose tolerance:

- They have both IFG and IGF.

- Both insulin resistance and impaired insulin secretion

Metabolic characteristics:

IGT&IFT have raised sugar levels in first 60 mts. IGT represents defective second phase insulin secretion.so continues to raise after 60 mts and remains elevated at 120 mts.

IFG starts with high FPG due to hepatic insulin resistance, but the incremental raise in plasma glucose at 30 – 60 mts is only slightly greater than normal glucose tolerant individuals. By 120 mts plasma sugar level will come to normal. IGT=> impaired second phase of insulin secretion and muscle insulin resistance resulting in less disposal of glucose during OGTT.

IFT	IGT
• Reduced hepatic insulin sensitivity • Stationary beta cell dysfunction and /or • Chronic low beta cell mass • Altered GLP-1 secretion • Inappropriately elevated glucagon secretion	• Reduced peripheral insulin sensitivity • Near – normal hepatic insulin sensitivity • Progressive dysfunction of beta cell function • Reduced secretion of GIP and • Inappropriately elevated glucagon secretion

CRITERIA FOR DIAGNOSIS OF DIABETES:

1. **HbA1c >6.5%** the test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay

OR

2. FPG>126mg/dl (7.0mmol/L) .fasting is defined as no caloric intake for at least 8 hours

OR

2Hour plasma glucose ≥ 200 mg/dl during an OGTT. The test should be performed as described by WHO using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water

OR

In a patient with classic symptoms of hyper glycaemia or hyperglycemic crisis, a random plasma glucose ≥ 200mg/dl (11.1mmol/l)

Characteristics	Type 1 DM	MODY	Type 2 DM in children
onset of age	Peak at 5 & 15 years	<25 years	Teenage years
Ethnic group	Caucasians	Caucasians	Hispanic, Asians, African American Mexican – America,
Male : female	1.1:1	1:1	1:1.5
Islet cell auto immunity	Present	Absent	Absent
HLA DR3, DR4	Very common	No increased frequency	No increased frequency
DKA	Common	Rare	Uncommon
Prevalence of obesity	Uncommon	Uncommon	≥90%
Mode of inheritance	Non mendalian, generally sporadic	Autosomal dominant	Non mendalian, but strongly familial
Number of genes controlling inheritance	Polygenic	Monogenic	Polygenic
Pathogenesis	Autoimmune beta cell destruction	Insulinopenia	Insulin resistance plus insulinopenia.
Long term course	Insulin dependent	Non-insulin dependent	Non-insulin dependent

EPIDEMIOLOGY OF DIABETES

Global burden of diabetes:

1) In 2012 371 million people had diabetes. The numbers to increase to 550 million by 2030.

2) There is a rising incidence of type 2 DM globally.

3) 80% of diabetic subjects live in low and middle income countries.

4) Greatest number of people with diabetes are between 40 – 59 years of age.

5) Almost 50% diabetics are undiagnosed. Diabetes causes 4.6 million death in 2011.

6) 78000 children develop type1 diabetes every year

Common form of diabetes and their prevalence:

Diabetes	Prevalence
Type1	~ 5%
Type2	~95%
Gestational	2 – 10 % of all pregnant women

Geographical distribution of Diabetes:

State	Author, year	Prevalence
North		
Kashmir	Zargar et al. 2000	6.1%
New Delhi	Prabakaran et al. 2005	15%
New Delhi	Ramachandran et al. 2005	10.3%
West		
Mumbai		
Jaipur	Ramachandran et al. 2001	9.3
		8.6
East	Gupta et al. 2003	
Guwahati		
Kolkata		
	Shaw et al.1999	8.3
South	Ramachandran et al. 2001	11.1
Thiruvanthapuram		
Hyderabad		
Bangalore		
Chennai	Raman et al. 1999	16.3
	Ramachandran et al. 2001	16.6
Ernakulum		
Vellore	Ramachandran et al. 2001	12.4
Tamilnadu		
	Ramachandran et al. 2001	13.5
	Mohan et al. 2006	14.3
	Menon et al.2006	19.5
	Ragupathi et al. 2007	3.7
	Ramachandran et al. 2008	18.6

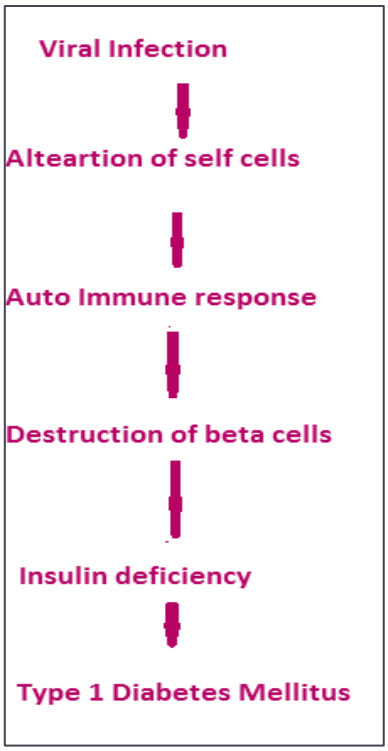
PATHOGENESIS OF TYPE 1 DM:

1) Auto Immune destruction:

Infiltration of lymphocytes in pancreatic beta cells causes type 1 DM

- After all beta cells are destroyed, the islets cells become atrophic
- deficiency of insulin secretion will occur due to immune mediated destruction of beta cells

PATHOGENESIS OF TYPE1 DM



- pancreatic α-cells is also abnormal in type 1 DM
- There is excessive secretion of glucagon in type 1 DM patients. Normally, hyperglycemia leads to reduced glucagon secretion.
- So in patients with type 1 DM patients glucagon secretion is not suppressed by elevated blood sugar level

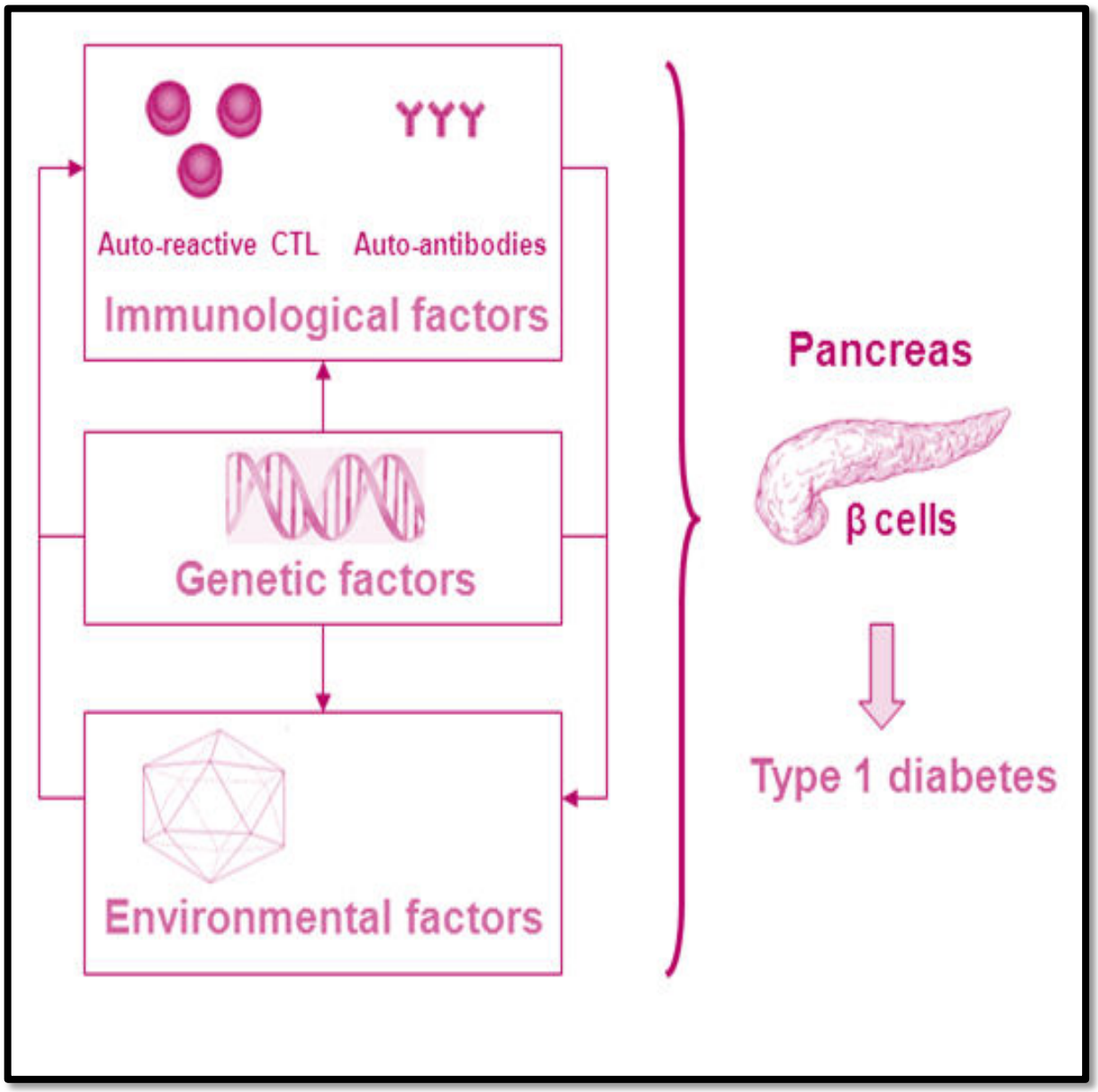
Abnormal level of glucagon worsen the metabolic derangements due to insulin deficiency.

Genetic considerations in Type 1 DM:

- Risk of diabetes is more with children born to diabetic parents
- Risk is around 3% when mother is affected, and is around 6% when father is affected
- Approximate empirical risk of development of type 1 DM up to the age of 25 years

First-degree relative with type1 DM	Risk of type 1 DM %
Father	2.5
Mother	1.5
Both parents	15 – 20
Mother and sibling	13
Sibling	3
Monozygotic twin	40

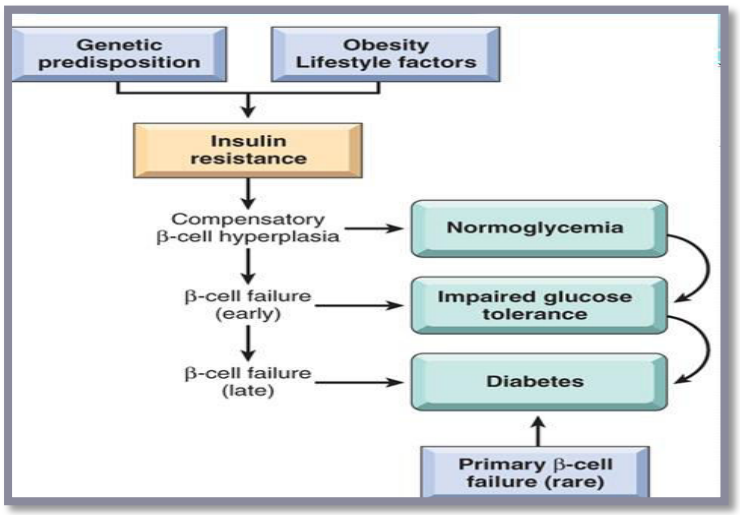
TYPE1 DIABETES MELLITUS-AN OVERVIEW OF ETIOLOGY



Pathology of Type 2 DM:

- Type 2 DM is defined by insulin resistance, abnormal insulin secretion that leads to abnormal fat metabolism and excessive hepatic glucose production,
- Pancreatic beta cells increase the insulin secretion to maintain the glucose tolerance in a near normal state in the early stage of this disorder.

As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. Then patient will develop IGT. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia.



PATHOGENESIS OF TYPE 2 DM

Insulin resistance:

- Insulin resistance is a state in which a given concentration of insulin produces a less-than-expected biological effect.
- Insulin resistance has also been defined as the requirement of 200 or more units of insulin per day to attain glycemic control and to prevent ketosis.
- Insulin resistance results from inherited and acquired influences.

Causes of Insulin resistance:

- ***Pre receptor:***
  - Anti-insulin antibodies
  - Abnormal insulin
- ***Receptor:***
  - Reduced number of receptors
  - Insulin receptor – blocking antibodies
  - Insulin receptor mutations
  - Reduced binding of insulin

- ***Post receptor:***
  - Mutations of GLUT4
  - Abnormal signal transduction

Combinations of defects:

Obesity is usually associated with post receptor abnormality and decreased number of insulin receptors. It is the common cause of insulin resistance.

Aging:

Aging is one the cause of insulin resistance - reduced production of GLUT-4 transporters

RISK FACTORS:

- Hypertension (BP >140/90 mmHg)
- History of GDM or delivery of baby >4 kg
- HDL cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl
- Obesity (BMI >25 kg/m^2)
- Polycystic ovary syndrome

- Race/ethnicity
- Habitual physical inactivity
- Family history of diabetes.
- Previously identified IFG or IGT

***Obesity and Type 2 Diabetes Mellitus*:**

- Free fatty acids and other fat cell products will be more in obese patients due to raised adipocyte mass.
- Insulin resistance in skeletal muscle and liver is due to overproduction of free fatty acids and adipokines.
- Free fatty acid impairs glucose utilization in peripheral tissues like skeletal muscles, promote glucose production by the liver, and impair beta cell function.
- Adipocytes secrete a number of biologic products (**Adiponectin, RB-4, TNF-α, and Leptin**). Adipokines regulate insulin sensitivity, body weight, and appetite.
- Insulin-sensitizing adiponectin, is decreased in obesity and this may causes hepatic insulin resistance.
- IL-6 and C-RP levels will be elevated due to adipocyte products and adipokines. They are inflammatory markers.

Genetic considerations in Type 2 DM:

- Environmental factors and genetic are the causes of insulin resistance and the beta cell dysfunction.
- Risk of development of diabetes is more in a person with diabetic parents; the risk is around 40% when both parents are affected.
- The disease is polygenic and multifactorial, environmental factors like obesity, smoking can modify the phenotype of an individual.
- The mechanisms of genetic alterations causing type 2 DM is not clear

Metabolic alterations in Diabetes Mellitus:

A) Glucose metabolism:

Increased hepatic output and decreased glucose utilization

Peripheral uptake- Reduced uptake of glucose in skeletal muscle, cardiac muscle and adipose tissue (GLUT- 4 receptors are insulin dependent)

Glycolysis:

- ❖ Reduced rate of phosphorylation in liver cells (Glucokinase is insulin dependent)
- ❖ Glycolytic enzymes are covalently modified by glucagon mediated c AMP cascade.

- ❖ Reduced availability of Fr 2,6 bisphosphate, reduced activity of PFK-1
- ❖ Reduced rate of glycolysis

Gluconeogenesis- Increased rate of gluconeogenesis due to -

- ❖ Increased availability of substrates

Increased activity and concentration of enzymes of pathway of gluconeogenesis under the effect of glucagon

Glycogen Metabolism- Enzyme activities are altered by glucagon triggered phosphorylation cascade.

- ❖ ***Glycogenesis-*** Inhibited due to reduced activity of glycogen synthase (Phosphorylated form is inactive form)
- ❖ ***Glycogenolysis-*** Stimulated due to increased activity of phosphorylase (Phosphorylated form is active form)

- ❖ ***TCA cycle-*** suppressed due to non-availability of oxaloacetate as it is channeled towards glucose production
- ❖ ***HMP Pathway-*** Suppressed due to reduced activity of glucose-6-P dehydrogenase enzyme as that is under the influence of insulin.

- ***Net effect-*** Elevated plasma glucose levels are due to raise in liver glucose production and increased insulin resistance.

Implications of altered carbohydrate metabolism:

- Hyperglycemia is a net effect of altered carbohydrate metabolism
- Glycosuria occurs once the glucose level crosses beyond the renal threshold
- Because of osmotic property of glucose, excess loss of water and electrolytes through kidney is termed as **polyuria**.
- Excess loss of water causes activation of the thirst mechanism (**polydipsia**).
- Increase in appetite and food intake (**polyphagia**) is due to negative caloric balance which results from tissue catabolism and glycosuria.

Metabolism of Lipids in Diabetes Mellitus:

A*) Adipolysis:*

- Triglycerides are mobilized rapidly from adipose tissue leading to raise in the levels of plasma FFA.

- ❖ Numerous tissues take up FFA including liver (except brain) and are metabolized to provide energy. As a result fatty acid oxidation will be increased.

Biochemical Basis of fatty acid oxidation:

- ❖ Normally, in the presence of insulin, the malonyl – CoA levels are high
- ❖ In the presence of high levels of malonyl-CoA, carnitine palmitoyl Transferase I levels will be low, so the transportation of fatty acyl-Co A's into the mitochondria will be reduced.
- ❖ Transport of fatty acyl-Co A's into the mitochondria will be increased in diabetic patient's due to low insulin state
- ❖ In mitochondria, FFA are get oxidized and producing acetyl-CoA which will be oxidized further in the TCA cycle.

Implication of high rate of fatty acid oxidation:

1) Ketosis

- o In the liver cells, large amount of acetyl-CoA is metabolized into the ketone bodies. e.g.; β-hydroxybutyrate Acetoacetate and Acetone,
- o Brain, Heart and Skeletal muscle utilize these ketone bodies for energy production

- There will be high levels of FFA and ketone bodies in DM, which will reduce the utilization of blood glucose and causes hyperglycemia.
- Ketoacidosis develops once the ketone bodies production exceeds utilization.
- Acetoacetate is get converted into acetate spontaneously and they are volatized by lungs producing odor. This is recognized by smell of breath.

Implication of high rate of fatty acid oxidation:

Hypercholesterolemia:

Excess Acetyl co A, the final product of FFA oxidation can enter the pathway of Cholesterol biosynthesis causing hypercholesterolemia, increasing the risk for atherosclerosis.

Serum Triglyceride levels:

- Lipoprotein lipase (LPL), an enzyme which is present on the surface of the, endothelial cells .Main action is to Cleave TGL
- LPL stores the free fatty acids in the adipocytes from circulation.
- LPL needs insulin for their action. So in the absence of insulin ,hypertriglyceridemia occurs

Net effect- Dyslipidemia (Atherogenic profile):

Increased level of circulating free fatty acids

Ketoacidosis

VLDL c and LDLC High

HDLc low (Inverse relation with triglycerides)

Hypertriglyceridemia

Hypercholesterolemia.

Protein metabolism in Diabetes Mellitus:

- Insulin increases the rate of protein synthesis and reduces the rate of protein degradation in our body.
- Insulin deficiency leads to increase in the protein catabolism.

Protein metabolism in Diabetes Mellitus (Net effect):

Increased catabolism of protein leads to elevated concentrations of amino acids.

- Hepatic and renal gluconeogenesis will be increased due to elevated concentration of amino acid precursors.
- This increased Hepatic gluconeogenesis causes further increase in the glucose production in type 1 DM

Advanced Glycosylation End Products:

Advanced glycosylation end products (AGEs) are the products which are produced from non-enzymatic glycosylation of extra cellular and intra cellular proteins.

- Interaction of excess glucose with amino groups on proteins causes non enzymatic glycosylation.
- They are cross-linked proteins (e.g., collagen), accelerate the rate of atherosclerosis, deteriorate renal function, decreases the synthesis of nitric oxide, induce endothelial dysfunction, and alter the structure and composition of extracellular matrix.
- AGEs levels correlates with the level of glycaemia, and these products tend to increase when renal functions declines.

Glycated hemoglobin:

Glucose and all the other sugar components with the free amino acid groups on the alpha and beta chains of hemoglobin is glycated by ketamine reactions due to hyperglycemia.

- These charge separated hemoglobin are collectively referred to as hemoglobin A_1 (HbA_1).
- The major form of HbA_1 is hemoglobin A_{1C} (HbA_{1c}) where glucose is the carbohydrate. **HbA_{1c} have 4–6% of total Hb A_1.**

- Other forms are glucose-6-phosphate (HbA_{1a2}),fructose-1,6 bisphosphate (HbA_{1a1});
- chronic hyperglycemia causes abnormal elevation of hemoglobin A_{1C} fraction in diabetic persons
- This test used to assess the glycemic control of an individual for the period of 2- 3 months.
- Glycated hemoglobin's are detected by following methods like gel electrophoresis and high pressure liquid chromatography
- Hemolytic anemia and hemoglobinopathies and uremia may interfere the estimation of Glycated hemoglobin.
- Glycated albumin levels are also used to assess the control blood sugar. they have limited value, because of shorter half-life (20-25 days)

Normal Hba1c level ---6-8%

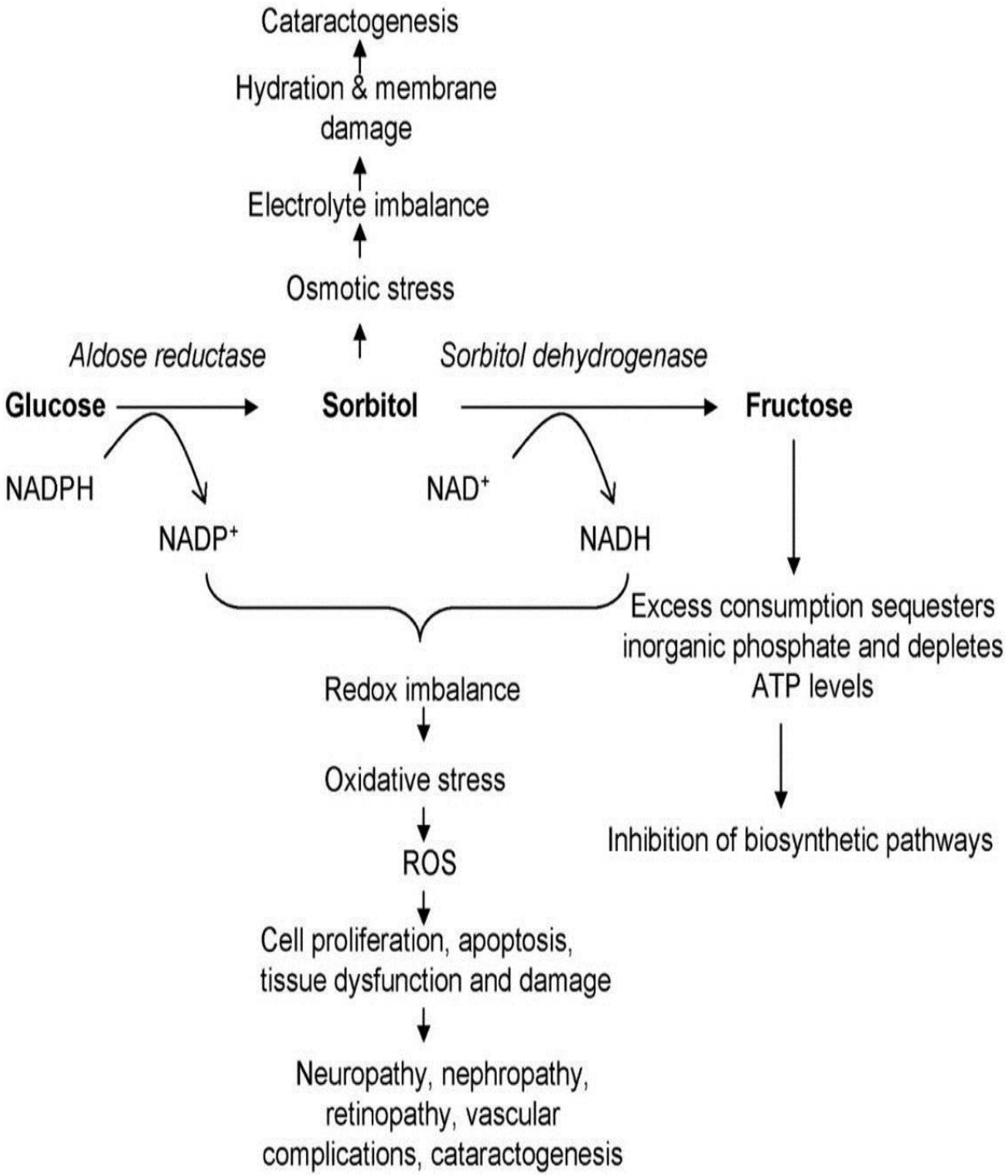
Fair glycemic control ---8-10%

Poor glycemic control ---10-12%

Very poor --- >12

Normal fructosamine level ---0.5-1.5 ng/dl

PATHOGENESIS OF COMPLICATIONS OF DIABETES



Metabolic syndrome definition

International diabetes federation definition
Central obesity (defined as waist circumference > 94cm for europid men and > 80cm for Europid women, with ethnicity specific values for other groups) Plus any two of the following four factors: • Raised TG level: 150 mg/dl, or with specific treatment. • Reduced HDL cholesterol: <40 mg/dl in males and < 50 mg/dl in females, or with specific treatment • Raised blood pressure: systolic BP>130mm/Hg or diastolic BP > 85 mm Hg, or normal Bp with specific treatment • Raised fasting plasma glucose (FPG) > 100 MG/dl, or previously diagnosed type 2 diabetes

Targets for treatment of the components of metabolic syndrome		
	High risk	very low risk*
Blood pressure(mm/hg)	**<135/85**	**<120/80**
Fasting glucose (mmol l^{-1})	**<6.1 (110mg/dl)**	**<5.6 (100mg/dl)**
2-h post-challenge plasma Glucose (mmol l^{-1})	**<10 (180 mg/dl)**	**<8 (144 mg/dl)**
Triglycerides (mmol l^{-1}) (<132mg/dl)	**<1.7 (<150mg/dl)**	**<1.5**
High – density lipoprotein	**<0.9 / >1.0**	**>1.0 / >1.1**
Cholesterol (mmol l^{-1})	**(35/39 mg/dl)**	**(39/43 mg/dl)**
*Confirmed Atherosclerosis Vascular Disease		

Medical nutrition therapy:

1) Diet planning

2) Exercise

Medical nutrition therapy is a component of preventing type 2 DM in individuals with IGT and for achieving glycemic control, weight reduction

RECOMMENDED DIETARY COMPOSITION FOR PATIENTS WITH DM:

Diet	Energy intake %
Carbohydrates	45-65
Sucrose	Up to 10
Proteins	10 -15
Fat	<30
n-6 PUFA	<10
n-3 PUFA	Consume oily fish once/ twice a week
MUFA	10 – 20
saturated fat	<10

Benefits of physical activity:

1) Improving Insulin sensitivity

2) Weight management

3) Improving bone density

4) Mental well being

5) Improving lipid profile

6) Improving blood pressure control

7) Improving cardio vascular function.

ORAL HYPOGLYCAEMIC :

The use of oral medications with diet & exercise can manage the problem but oral hypoglycaemics are not insulin & therefore cannot replace insulin.

Oral hypoglycemics help the body to utilise or make insulin.

- Beta cells must make enough insulin to work, otherwise combination with insulin is necessary.

Classes of Oral Hypoglycaemic Agents:

Target insulin secretion:

- Sulphonylureas (glibenclamide)
- Meglitinides (repaglinide)

Target insulin resistance:

- Biguanide (metformin)
- Thiazolidinedione's (rosiglitazone)

Target glucose absorption from intestine:

- Alpha glucosidase inhibitors (acarbase)

Biguanide: Metformin

Decreases hepatic glucose output

Increases peripheral uptake of glucose into cells

Monotherapy or adjunct

Does not produce weight gain, useful in obese patients.

Dose:

- 500mg od increasing gradually to 500mg tds
- Max dose 3gm per day – but most of the patients tolerate 2gm.

Reduces HbA1C by 1-2%

Contraindications:

- May provoke lactic acidosis
- Contraindicated with Renal impairment
- Liver & heart failure and in Severe dehydration

Side effects:

- Nausea, vomiting, diarrhoea, abdominal discomfort, impaired B_{12} absorption

Sulphonylureas:

Stimulate beta cells to release insulin from functioning pancreatic cells

Examples:

Glibenclamide (Daonil, Glimel)

- Widely used, long acting

- Avoid in elderly, Renal impairment

Gliclazide (Diamicron, Nidem)

Glipizide (Minidiab, Melizide)

Glimepiride (Amaryl, Dimirel)

Dose: varies per drug

Drug interactions: multiple

Reduces HbA1C by 1-1.5%

No lag in response.Drug of choice in lean patients. Drugs are broken down in liver so avoided in people with liver and renal impairment

Adverse Effects:

GI disturbances, headache; bone marrow depression

Mild skin reactions, photosensitivity, mild alcohol intolerance.

Hypoglycaemia

Weight gain

5-10% secondary failure rate / year

Long Term Side Effects are exhaustion of Beta cells. Secondary failure of treatment is high Therefore, use Short-acting versions at lowest

effective doses. Secondary failure is inevitable ,after many years of treatment

Alpha Glucosidase Inhibitors

Reduces glucose absorption from the gut by inhibiting the breakdown of disaccharides to monosaccharaides such as glucose.

Only effective if taken at same time as food, as drug needs to reach intestines at same time as food to work.

Example:

Acarbose (Glucobay)

Monotherapy or adjunct

Dose:

50mg OD increasing gradually to TDS, dose can be increased up to 200mg TDS. Take with or just prior to meal

Side effects:

flatulence, diarrhoea, abdominal distension & pain

Contraindications

Pregnancy / breast-feeding

Liver and severe renal impairment

Inflammatory bowel disease & intestinal obstruction

In therapy:

Add-on to treatment with metformin or sulphonylureas

Part of triple therapy

Monotherapy

With insulin in Type 1 diabetes

- Reduces HbA1C by 0.5%. relatively Safe.it has weight neutral property
- Dose coupled with meals
- Monitor LFT during 1st 6-12mths

Meglitinides:

Prandial Glucose Regulators (PGR's)

Stimulate beta cells to release insulin, response however is glucose dependent

Following meals there is an early phase insulin release

In Type 2 diabetes, this is lost causing post prandial spikes

PGR mimic release of physiological insulin, as they are short acting and do not stimulate the beta cells constantly

Repaglinide (NovoNorm)

Dose: initially 500mcg, up to 4mg as a single dose

Tablets should be taken 30 mins before a main meal

Contraindications:

Diabetic ketoacidosis

Pregnancy & breast feeding

Type 1 diabetes

Severe hepatic impairment (repaglinide only)

Monitoring: LFT periodically

Repaglinide: 500mcg, dose can be modified according to response every 1-2weeks; dose can be increased up to 4mg as a single dose, max 16mg daily.

Nateglinide: initially 60mg tds, adjusted according to response up to max 180mg tds

Quickly lowers post prandial glucose levels (no lag before response)

↓HbA_1C 0.5-2% .it has short half-life. Meal time flexibility

↓Risk of weight gain

Thiazolidinediones:

Improves insulin sensitivity skeletal muscle, adipose tissue & liver, thereby promoting uptake of fatty acids & glucose at these sites .Counteract insulin resistance .Reduces HbA_1C by 1-2%.Beneficial effect on lipids

Examples:

Pioglitazone(Actos), Rosiglitazone (Avandia)

Adjunct with either SU or metformin

Dose: varies per drug

Pioglitazone (Actos): 15-30mg once daily

Rosiglitazone (Avandia): 4 mg/day, or + metformin 8 mg/day

Contraindications:

Pregnancy / breast-feeding

Liver impairment

Heart failure

Side-effects:

Dizziness

Oedema,

Headache,

Weight gain.

Optimal Glycemic Control:

-One of the primary goals in treating diabetes is to 'treat to target' in terms of HbA_1C

-With long term treatment, 75% of patients do not maintain optimal glycemic control (<7% HbA_{1c}) with monotherapy alone[1]

-Optimal combinations of oral therapy to treat diabetes need to be found to achieve this target

-Combination therapy used when monotherapy fails

Insulin therapy, or

Insulin therapy + metformin, or

Insulin therapy + sulphonylurea

Monitor glycaemic control :

Target HbA1C = 7%

Many oral treatment options

Change therapy in response to poor control

Insulin

Metabolic benefits of insulin therapy
• Reduces fasting and postprandial glucose levels • Suppresses hepatic glucose production • Stimulates peripheral glucose utilization • Increases glucose oxidation/storage in skeletal muscles • Improves abnormal lipoprotein composition • Reduces glucotoxicity • Improves endogenous secretory ability • Reduces glycosylated end products

Anti-catabolic effects of insulin (inhibits)		
Liver	muscle	adipose tissue
Glycogenolysis	proteolysis	lipolysis
Gluconeogenesis	amino acid output	
Fatty acid oxidation		
Ketogenesis		
Proteolysis		

Anabolic effects of insulin (promotes)		
Liver	muscle	adipose tissue
Synthesis	uptake	uptake
Glucagon	glucose	glucose
RNA	amino acids	protein
Amino acids		
Fatty acids	synthesis	synthesis
Triglycerides	glycogen	glycerol
Protein		fatty acids
triglycerides		

Types of Insulin:

Source:

- Animal sources
- Recombinant DNA = human insulin

Duration of action:

- Rapid acting
- Short acting
- Intermediate acting
- Long-acting
- Biphasic

Rapid-acting Insulin:

Rapid acting = analogue insulin

Examples

- Humalog (Lilly)
- Novorapid (Novo Nordisk)

Very rapid onset approx 15 mins;

- ensure food intake after administration

Peak action 1 hour, duration of action 4 hours

Can be administered just before or even after meals

Hypoglycaemic effect over in < 3 hours

Clear solution

Only form that can be given IV

May be combined with longer acting insulin

Short-acting Insulin:

Short acting = neutral or soluble insulin

Rapid onset of action (30-60 mins)

ensure food intake ½ hour after administration

Peak 2-4 hours, duration 6-8 hours

Examples

Human Actrapid (Novo Nordisk)

Humulin R (Lilly)

Hypurin Neutral (Beef) (Aspen)

Injected < 30 mins before meals

Clear solution

Intermediate-acting Insulin:

Intermediate acting = isophane insulin (NPH)

Cloudy due to the addition of a protein

- (isophane or zinc)

Must be mixed well before use

Examples:

- Humalin NPH
- Hypurin Isophane
- Protophane
- Levemir – Detemir,

Retarded onset = 1–2 hrsPeak 4-12 hours

Prolonged duration of action lasting 8-20 hrs

Always draw up clear before cloudy if 2 types of insulin are required

Long-acting Insulin:

Lantus –Glargine Insulun- Once daily

Duration of action 24 hrs; Peakless (Clear)

Biphasic Insulin:

Mixture of soluble or analogue insulin and isophane

Offer double insulin release profiles from single injection form.

Examples:

- Humalog Mix 25 or Mix 50 (Lilly)
- Human Mixtard 10/20/30/40/50 (Novo Nordisk)
- Novomix 30 (Novo Nordisk)

Insulin Regimens:

Variety of insulin regimens

- Tailored to meet the needs of different people with diabetes

Treatment option chosen reflects

- Type of diabetes
- Person's lifestyle, age and ability to self-test blood glucose
- Presence of obesity
- Choice

Goal is insulin release profile most similar to physiological state.

Once-Daily:

long-acting basal or intermediate acting insulin

insulin should be given at breakfast

Simplest regimen

Sufficient for many elderly Type 2 people

Often used in combination with OHA

Obese Type 2 person uncontrolled on maximal doses of oral therapies

- Example: Metformin + once daily insulin

Twice-Daily:

Twice-daily biphasic insulin

Very popular regimen

Often used in treatment of Type 2 diabetes

Administered in morning and at teatime

Can be quite restrictive as meal times cannot be varied

Basal-Bolus:

Four daily injections

- Before meals (bolus)

3 short- or rapid-acting insulin doses

– Bedtime (basal)

Once-daily intermediate-acting insulin

– Can adjust bolus injections for eating patterns

Three Times Daily:

– Mixture of short- and intermediate-acting insulin before breakfast

or

– Mixture of short-acting insulin before the evening meal or

– Intermediate-acting insulin at bedtime

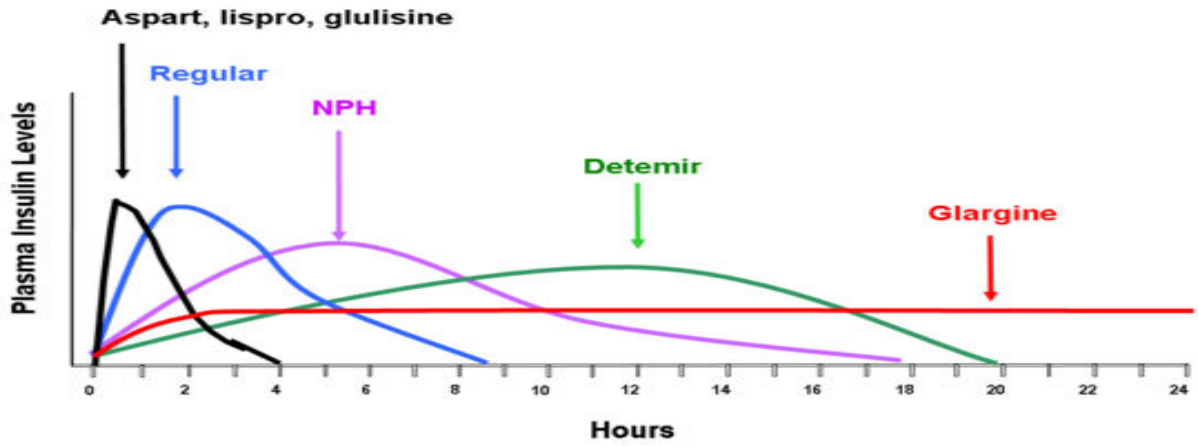
Regimen often adjusted depending on the person's circumstances

Flexibility offered to the prescriber

Approximate time – course of action of various insulin preparations

Kind of insulin Preparation	onset of action (hr)	peak of activity (hr)	total duration of action (hr)
SHORT ACTING*			
Regular	0.5-1	2-4	4-6
Semilente	1-2	3-6	8-12
INTERMEDIATE ACTING*			
NPH	3-4	10-16	20-24
Lente	3-4	10-16	20-24
*LONG ACTING**			
PZL	6-8	14-20	32
Ultralente	6-8	14-20	32
*BIPHASIC***			
PREMIXED (NPH + REG)	0.5	2-10	12-18
ANALOGUES			
SHORT ACTING	within a few	1	4
Lispro (Humalog)	minutes		
Aspart (Novolog)			
Glulisine (Apidra)			
LONG ACTING			
Glargine (Lantus)			
Detemir (Levemir)	----------Peak less action for 24 hrs----------		
PREMIXED			
Novomix 30/70			
Humalog mix (25:75 & 50:50)			

DURATION OF ACTION OF VARIOUS INSULINS



Factors affecting the disposal of injected insulin
Injection site a. Anatomic site b. Exercise c. Depth d. Insulin concentration e. Mixing insulin preparations f. Local tissue degradation g. Intra – subject coefficient variation Plasma a. Antibody binding and release of insulin b. Physical state of modified insulin in serum Insulin receptors

a. Final disposal of insulin by liver, and kidney cell – surface receptors

Adverse Effects of insulin:

Hypoglycemia

Allergic reactions,

- usually local site & usually diminish
- less likely with human insulin

Insulin lipodystrophy

- Atrophy or hypertrophy of subcutaneous fat at injection sites
- Rotate within sites to prevent

Insulin insensitivity or resistance

- Requires higher doses of insulin

Hypoglycemia

ADA definition of hypoglycemia:

AMERICAN DIABEDES ASSOCIATION group on hypoglycemia in diabetes as "all episodes of abnormally low plasma sugar concentration that expose the individual to potential harm".

Clinical classification:

1) Severe hypoglycemia
2) Documental symptomatic hypoglycemia
3) Asymptomatic hypoglycemia
4) Probable symptomatic hypoglycemia
5) Relative hypoglycemia

1) severe hypoglycemia:

Those who need active medical intervention like administration of carbohydrate glucagon for the hypoglycemia episodes is known as severe hypoglycemia

2) Documental symptomatic hypoglycemia:

Patients developing symptoms of hypoglycemia in the plasma glucose concentration of ≤70 is known as documented symptomatic hypoglycemia

3) Asymptomatic hypoglycemia:

Patients with atypical symptoms of hypoglycemia with plasma sugar concentration of ≤ 70 mg/dl is known as asymptomatic hypoglycemia

4) Probable symptomatic hypoglycemia:

Patients with typical symptoms of hypoglycemia plasma glucose concentration of ≤ 70mg/dl is known as *probable symptomatic hypoglycemia.*

5) Relative hypoglycemia:

Diabetic patients with typical symptoms of hypoglycemia with plasma glucose concentration of ≤ 70 mg/dl is known as relative hypoglycemia

Classification of Hypoglycemia

1. REACTIVE HYPOGLYEMIA (Post prandial Hypoglycemia)

a. Post – gastrectomy
b. Early stage of maturity onset diabetes
c. Inborn errors off metabolism (e.g. Hereditary Fructose intolerance & galactosemia
d. Idiopathic post prandial syndrome

2. FASTING HYPOGLYCEMIA

A. DEFICIENT GLUCOSE PRODUCTION (NORMAL INSULIN LEVEL)

1. Hepatic Dysfunction

a. Glycogen storage disease
b. Advanced stage of storage disease
c. Hepatoma

2. Endocrine dysfunction

a. Addison disease
b. Hypopituitarism
c. Glucagon deficiency

3. ***Sepsi***s

a. Cytokines associated to endotoxinemia increase insulin release.

B. OVER UTILIZATION OF GLUCOSE (ELEVATED INSULIN LEVELS)

1. Hyperinsulinemia

a. Insulinoma
b. Nesidioblastosis
c. Auto antibodies against insulin or insulin receptor

2. ***Inappropriate insulin level:***
   a. The extra pancreatic tumors
   b. Cachexia with fat depletion
   c. Systemic carnitine deficiency

C. SUBSTRATE DEFICIENCY
   a. Chronic starvation
   b. Chronic renal failure
   c. Ketotic hypoglycemia of infancy

D. COMPROMISED GLUCOSE COUNTER REGULATION

1. ***Fixed syndrome***
   a. Defective glucose counter regulation
   b. Hypoglycemic unawareness

2. ***Dynamic syndrome:*** Elevated blood glucose thresholds resulting from
   a. Effective intensive insulin therapy
   b. Recent antecedent hypoglycemia
   c. Therapy with a adrenergic antagonist

3. ***Drug induced hypoglycemia***
   a. Exogenous insulin (iatrogenic, fictitious)
   b. Sulfonylurea
   c. Miscellaneous – Salicylates, Propranolol, Tranquilizer
   d. Toxins - Pentamide, Quinine etc.

Pathophysiology:

- Human brain consumes 5 gms glucose per hour

- Blood supply to brain is around 1 L/mt.

- It can reserve around 1.5 gms of glycogen as reserve

- When blood sugar level falls below 45 mg/dl, the hypothalamic center get activated and sending signals to following centers

1) Hunger Center

2) Bulbar reticular system leading onto activation of sympathetic and parasympathetic system.

3) Pituitary leading on to release of ACTH, GH.

These changes causes gluconeogenesis and raise in blood sugar level.

SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

Clinical Signs and Symptoms of Hypoglycemia	
Sympathetic / parasympathetic Activation	**Neuroglycopenia**
Clinical signs and symptoms of Adrenergic activation Pallor, tremor, palpitations of anxiety Acute sensation of hunger Occasionally hypothermia, vomiting, fever, moderate tachycardia, crisis of systolic hypertension a. Clinical signs and symptoms of parasympathetic activation Nausea and eructation Cold sweating Mitigation of expected tachycardia or true bradycardia Mild hypotension	**Clinical signs and symptoms of neuroglycopenia** Headache, dizziness, fatigue, irritability or apathy and lethargy Frequency yawning and perioral numbness Disturbed vision and diplopia Paresthesia and motor dysfunction Cognitive impairment, mental confusion and inebriation Personality changes, psychotic behavior Occasionally transient hemiparesis or focal neurologic deficits Convulsions (in children simulating true crisis of epilepsy) Semi – coma, coma and even death

PREDISPOSING FACTORS IN DRUG INDUCED DIABETIC HYPOGLYCEMIA:

Predisposing factors in drug – induced diabetic hypoglycemia	
Under nutrition or omission of food or Starvation Unexpected exercise Renal or Hepatic dysfunction Abuse of alcohol Acute sickness Erroneous high insulin or sulfonylurea doses Increased absorption of insulin from the site of injection	Administration of a β-blocker Defective counter regulation, hypoglycemia unawareness Lowered glycemic threshold for hypoglycemia and counter regulation during intensive insulin treatment (with compromised recognition of developing hypoglycemia)

Hypoglycemic unawareness:

Failure of an individual to develop autonomic symptoms of sweating, tremor, hunger.

These symptoms usually absent in 20 – 50% of long standing type 1 DM

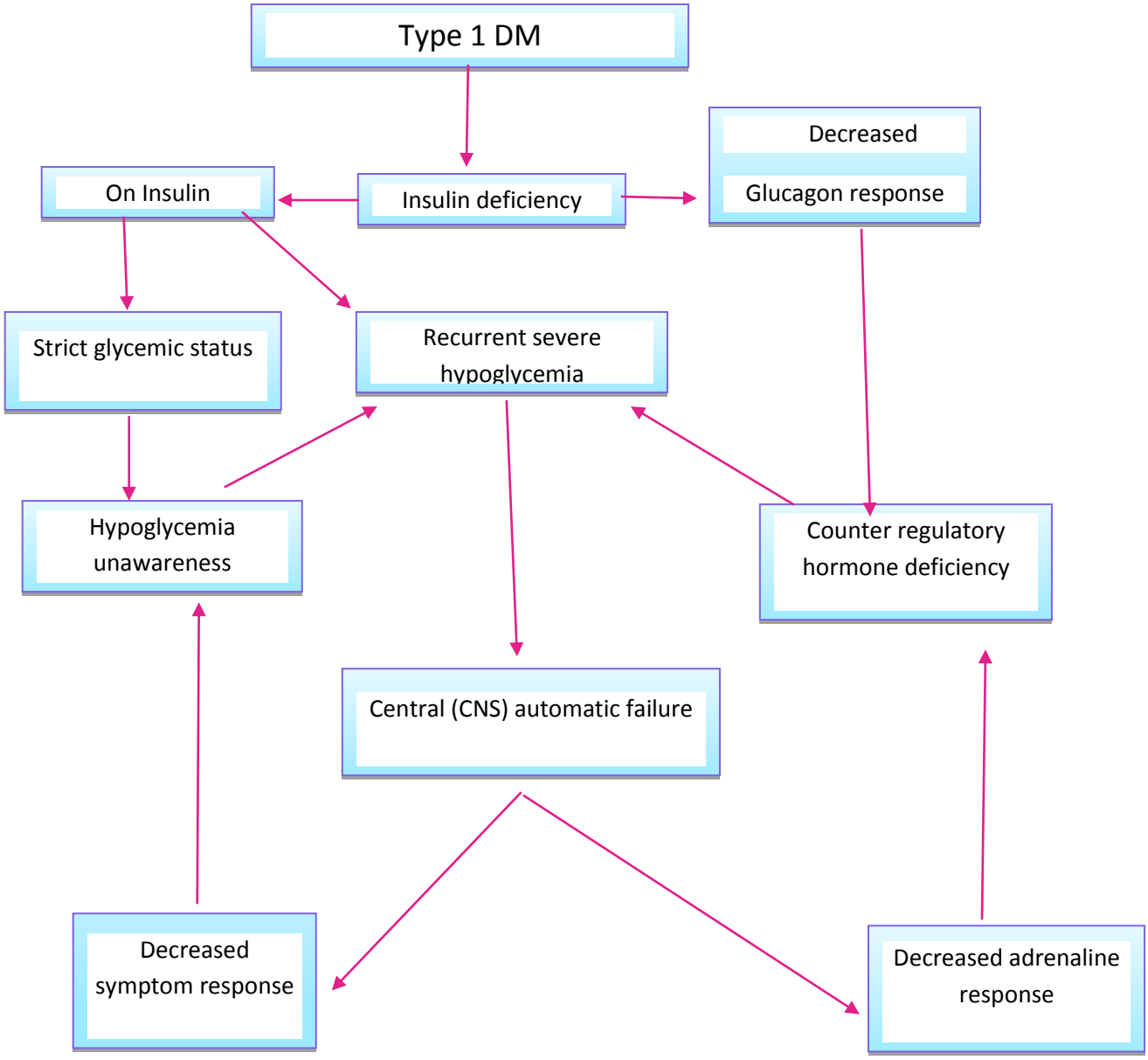
Classical features:

- One episode of hypoglycemia confers increased risk of subsequent episodes of hypoglycemia
- Recent episode of hypoglycemia reduces the sympathetic response to subsequent hypoglycemia
- Beta blocker should be used cautiously in DM patients. because they will increase blood glucose threshold for symptoms of hypoglycemia by blocking adrenalin action

Diagnosis:

Diagnosis mainly based on "whipple's triad"

1) Low plasma glucose concentration
2) Symptoms of hypoglycemia
3) These symptoms relived by correction of blood sugar level



Sequence of Events in the development of Hypoglycemia – associated Autonomic Failure

Hypoglycemic variants

1) Somogyi phenomenon

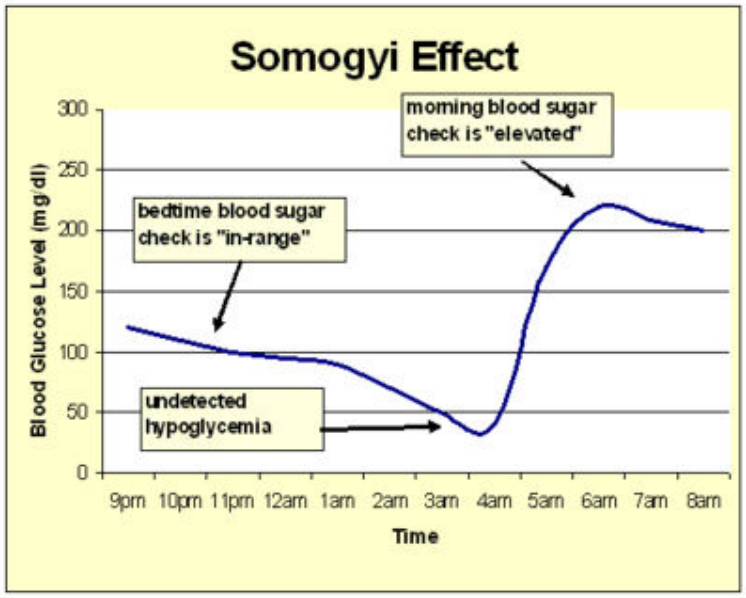
2) dawn phenomenon

Somogyi:

Post Hypoglycemic Hyperglycemia.

Hypoglycemia induced hyperglycemia due to increased secretion of counter regulatory hormones.

If the insulin dose is increased beyond the amount required for any given portion of a day, there is a counter regulatory hormone response, resulting in hyperglycemia. Reduction of insulin dose is advised in such a situation

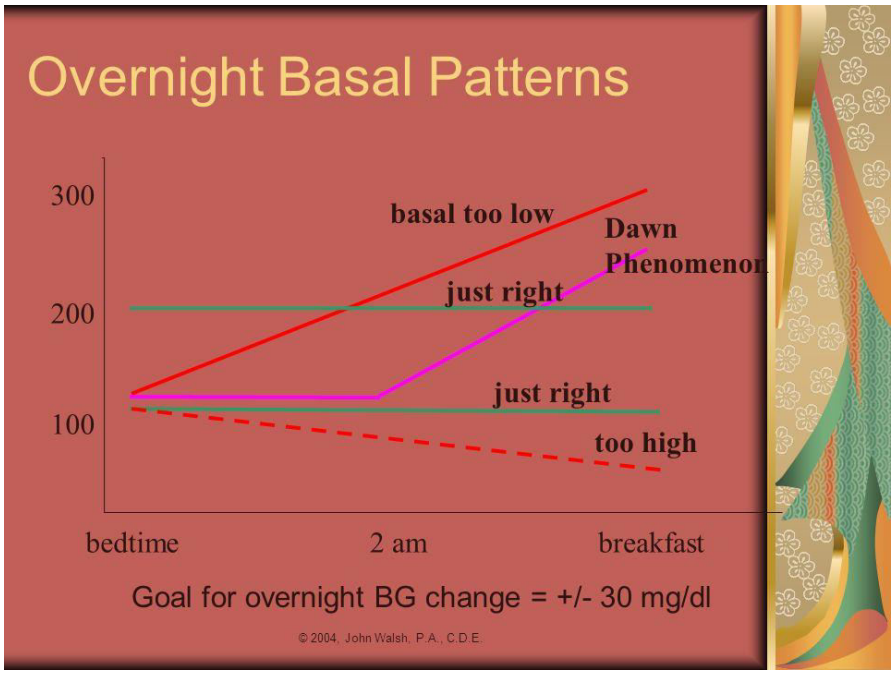


Dawn phenomenon:

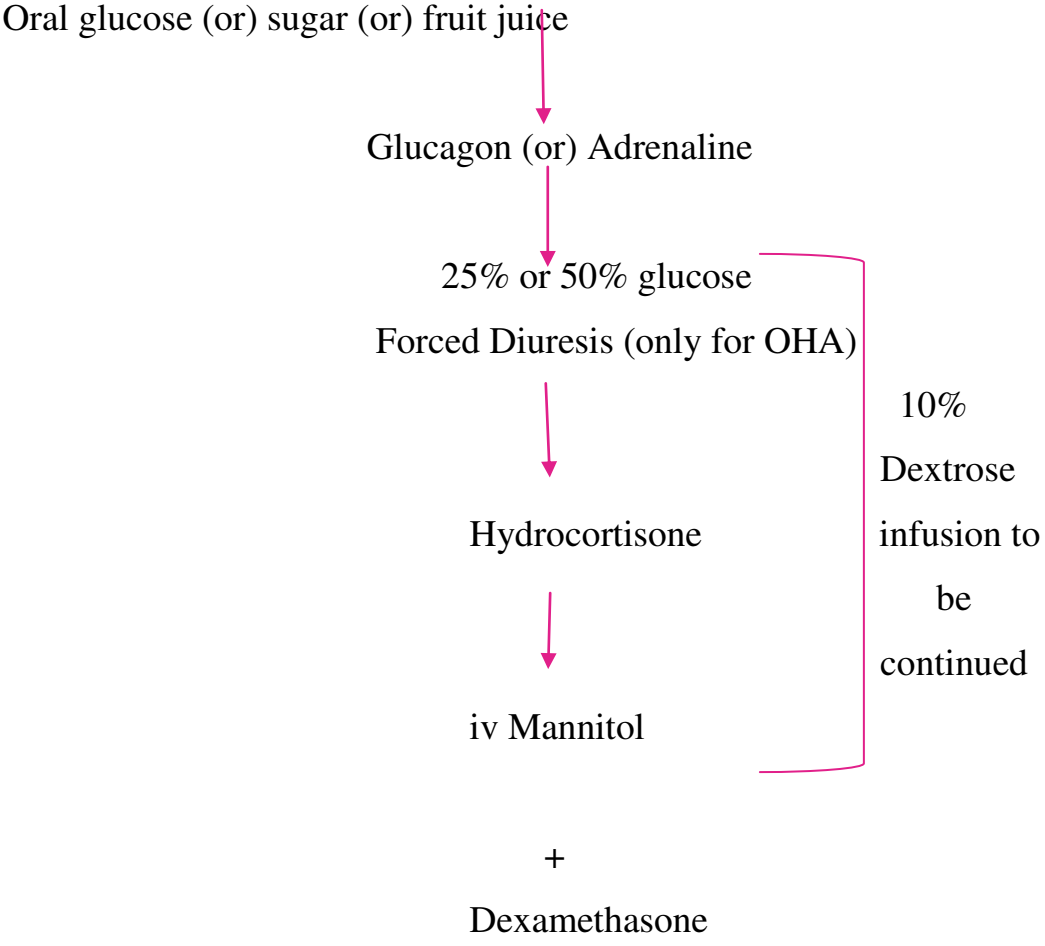
Dawn => high fasting blood sugar.

Many patients with type 1 DM demonstrates early morning 4 – 8 A.M hyperglycemia that is aggravated again by intake of food during break on fast.

This could be due to peripheral utilization or increased hepatic glucose production or both. In this condition excess of insulin is needed to control hyperglycemia. Early morning blood sampling at 3 A.M is necessary to differentiate both these conditions.



STEP CARE TREATMENT FOR HYPOGLYCEMIA



MECHANISM LINKING DIABETES AND CARDIOVASCULAR DISEASE:

1) Adipokines:

These are produced from adipose tissue

Adipokine	Actions
Adiponectin	Anti – inflammatory and anti atherogenic properties Low levels characteristic of persons at increased risk of diabetes Decreases uptake of oxidized LDL Decreases monocyte adhesion to endothelial cells Decreases expression of adhesion molecules Decreases proliferation and migration of vascular smooth Muscle cells
Leptin	Regulates energy intake and expenditure Enhances cellular immune responses Increases blood pressure levels
angiotensinogen and angiotensin II	Vasoconstrictive Enhances the formation of foam cells Stimulates intracellular adhesion molecule-1,vascular cell adhesion molecule-1, MCP-1, M-CSF expression in the cells of the vessel wall increases monocyte-macrophage platelet activity in the vessel wall Endothelial dysfunction
Tumor necrosis factor(TNF)	Expression of adhesion molecules on the surface of the endothelial cells and VSMCs
Plasminogen activator inhibitor-1 (PAI-1)	Inhibits the breakdown of fibrin clots promotes thrombus formation

2) Endothelial dysfunction:

The normal endothelium maintains the normal vasomotor tone and balancing coagulation cascade.

- Stimulation of insulin receptors activates P1 R-3, there by producing nitric oxide, leading on to vasodilation, which also having anti-inflammatory, antithrombotic and atherogenic properties.

- In diabetics during hypoglycemic episodes, endothelial cells secretes endothelin – I, that produces vasoconstriction, increasing vascular permeability, VSMC proliferation

VSMC migration and proliferation:

Insulin resistance initiates pro atherogenic cellular events - proliferation and migration of smooth muscles

Monocyte/ macrophage adhesion and migration:

Insulin receptor found in monocyte /macrophage molecules. So insulin resistance increase macrophage apoptosis.

There by accelerating the development of vascular lesion and contribute to plaque rupture.

Insulin resistance:

- Insulin resistance syndrome:

1) Hypertension
2) Dyslipidemia
3) Hyper coagulable state

- Insulin resistance increases the atherosclerotic plaque formation. So it is an independent risk factor for atherosclerosis. Usually insulin resistance precedes; 10-15 years after the development of type 2DM. Insulin resistance can be measured by ***HOMEOSTASIS MODEL ASSESSMENT METHOD***

HOMA – IR = sr.Insulin * sr. Glucose /22.51

- One unit increase in HOMA - IR -→ 5.4 % increases risk for cardiovascular disease.

Q-T INTERVAL

QT interval=> duration of ventricular electrical systole

- Measured from beginning of QRS complex to end of 'T' wave.
- Because of practical difficulties in measuring Q-T interval, American heart association electrocardiography and arrhythmia committee recommends global measurements of intervals, including QT from all 12 leads

QT interval in precordial leads depends on:

1) Proximity of leads with heart.
2) Local repolarization duration at the site of facing the recording electrode.

QT dispersion => difference between the shortest * longest QT interval among standard leads

QT interval decreases with increasing heart rate, Bazett's formula used to calculate corrected QT

$$QT = QT/\sqrt{RR}$$

Normal QT interval in male – 0.397 s

Female - 0.415 s

Normal corrected QT interval M = 0.440 s

F = 0.460 s

Main problem in bazett's formula is that will overcorrect at rapid heart rate. So they introduced other formulas. But none of them are significant.

Framingham study was conducted in 5000 adults aged 28-62 yrs. for calculating QT interval. Which is superior to bazett's & other formula

Q-T interval variation:

- Q-T interval is more in the evening & at night
- Sleep prolongs the Q-T interval by 18msec at heart rate 60 and by 21ms at a heart rate of 50 beats/mt. This is due to autonomic tone

Causes of QTc interval prolongation:

- During sleep
- Hypothermia
- Acute MI

- Hypocalcaemia
- acute myocarditis
- procainamide effect
- quinidine effect
- cerebral injury
- HOCM
- Pulmonary embolism
- Increased ICT
- MVP
- Hypothyroidism
- Complete block with torsade pointe

MATERIALS AND METHODS

DESIGN OF STUDY:

Observational study.

PERIOD OF STUDY:

10 months (JANUARY2014 TO OCTOBER2014)

SELECTION OF STUDY SUBJECTS:

This study is to be conducted in diabetic patients who are all admitted in medical ward with symptoms of severe hypoglycemia at Govt. Rajaji Hospital, Madurai. Severe hypoglycaemia was defined in this study, as the condition requiring active medical intervention such as carbohydrate administration when plasma sugar level was <60 mg/dl.

STUDY POPULATION:

100 cases

ETHICAL CLEARANCE:

CONSENT: Individual written and informed consent.

ANALYSIS: STATISTICAL ANALYSIS.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: NIL

INCLUSION CRITERIA:

- Type 2 DM & Type1(in all age groups)

EXCLUSION CRITERIA:

- Patients with electrolyte abnormalities.
- Coronary artery disease.
- Concurrent use of drugs which causing Q-T prolongation (quinidine, procainamide, Tri & Tetra cyclic antidepressant).

ANTICIPATED OUTCOME:

Prolongation of corrected Q-T interval during the episodes of hypoglycemia (Normal QTc M=440ms, F=460ms)

DATA COLLECTION:

100 cases were selected for the study after applying the inclusion and exclusion criteria as stated above and subjected to following baseline data and clinical characteristic line

The baseline characteristics of the patients- age, sex, diabetic (both type 1 and type 2) patients with symptoms of hypoglycemia with low glucose level , duration of diabetes, Q-T interval were recorded in proforma prepared according to need of study.

Corrected Q-T interval was calculated by using bazett's formula

LABORATORY INVESTIGATION:

RBS (Venous blood sample for glucose analysis).

Sr. Electrolytes and

Sr. Calcium

OTHER INVESTIGATIONS:

ECG

ECHOCARDIOGRAM

RESULTS

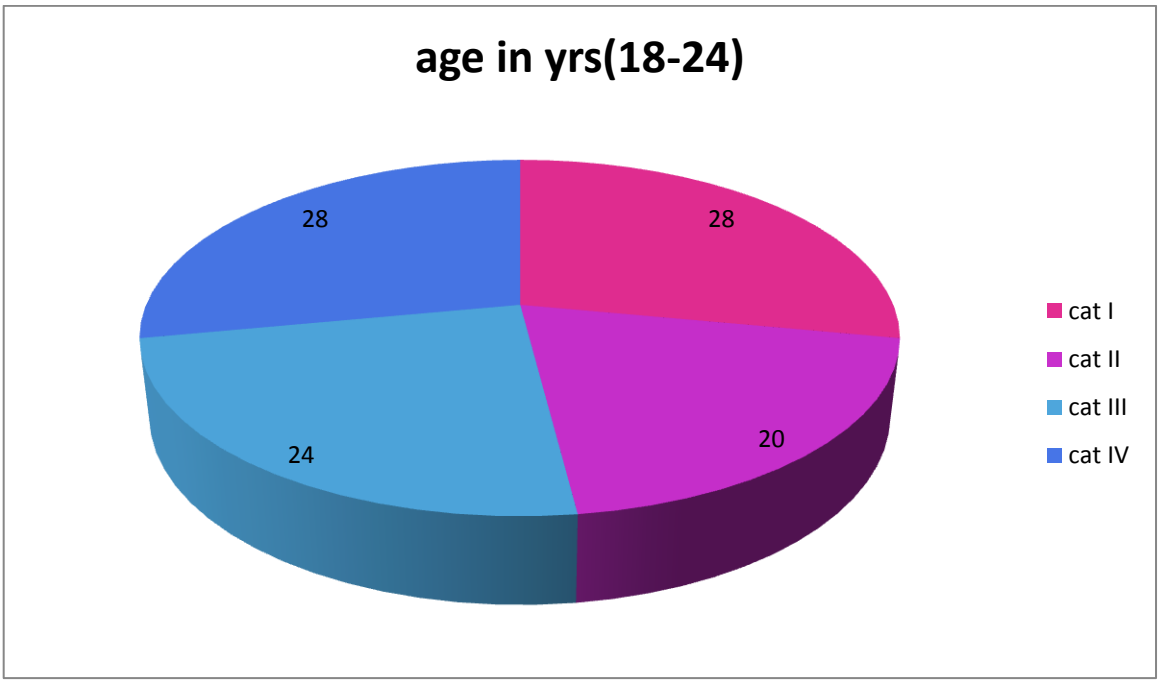
AGE DISTRIBUTION IN HYPOGLYCEMIA:

Sugar level(mg/dl)	Age in years(18-74yrs)
Cat I(60-50)	28
Cat II(40-49)	20
Cat III(30-39)	24
Cat IV(<30)	28
Total	100

Comments:

In our study 48 patients had hypoglycemia in the range of 60-40 mg/dl, and 52 patients had hypoglycemia below 40

AGE DISTRIBUTION IN HYPOGLYCEMIA:



Category I – blood sugar level 60-50mg/dl

Category II – blood sugar level 40-49mg/dl

Category III- blood sugar level 30-39 mg/dl

Category IV- blood sugar level <30 mg/dl

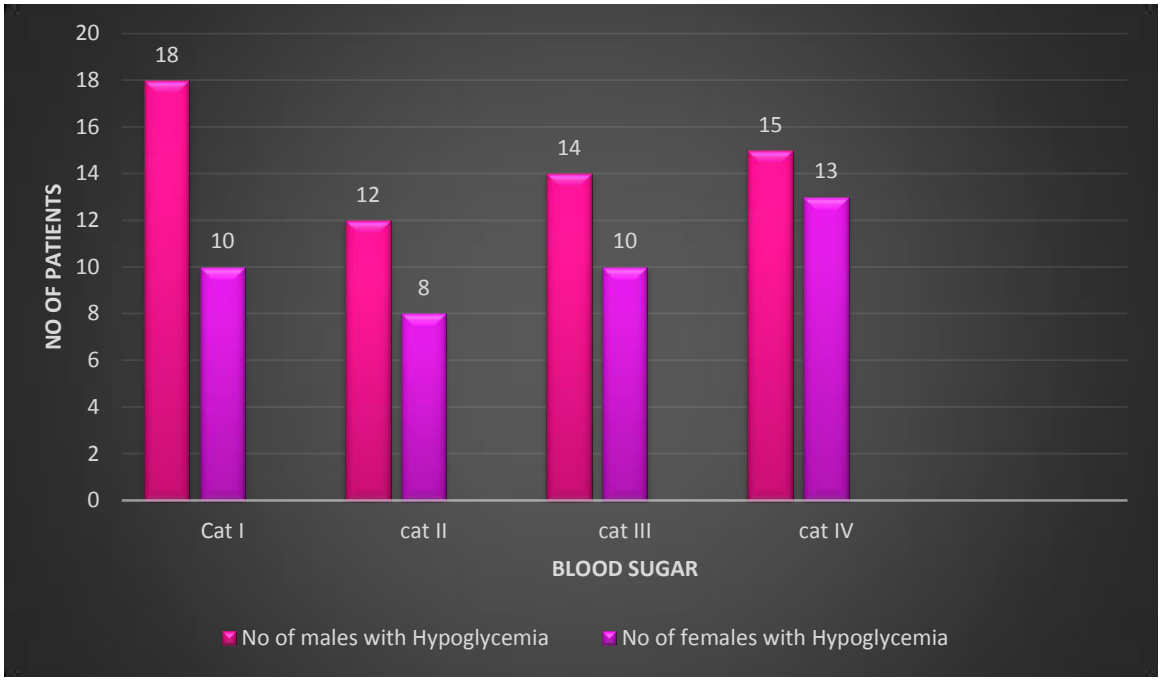
SEX DISTRIBUTION IN HYPOGLYCEMIA:

Sugar mg/dl	Male (%)	Female (%)	Total
Cat -I	18(30.50)	10(24.39)	28
Cat -II	12(20.33)	8(19.51)	20
Cat -III	14(23.72)	10(24.39)	24
Cat- IV	15(25.42)	13(31.70)	28

Comments:

59 males 41 females had hypoglycemia in our study. So incidence of hypoglycemic more in male population in our study.

SEX DISTRIBUTION IN HYPOGLYCEMIA:



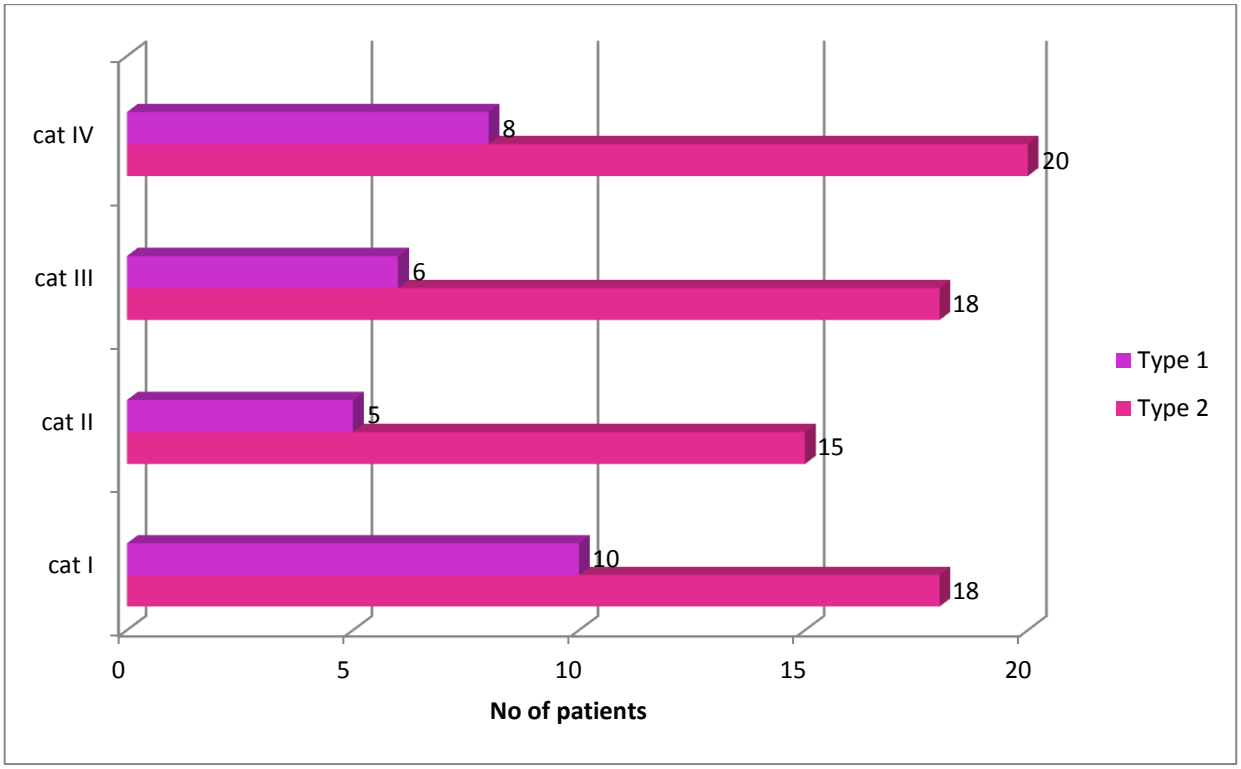
INCIDENCE OF HYPOGLYCEMIA IN TYPE-2 AND TYPE-1 DIABETES:

Sugar	TYPE – II	TYPE – I	Total
Cat- I	18 25.35%	10 34.48%	28
Cat -II	15 21.12%	5 17.24%	20
Cat -III	18 25.35%	6 20.68%	24
Cat- IV	20 28.16%	8 27.58%	28
	71	29	100

Comments:

In our study, 38 male and 14 females of type-2 DM Patients are had hypoglycemia below 40 mg/dl. 33 males and 15 females of type 1 DM patients had hypoglycemia in the range of 60-40 mg/dl. Among diabetes males are commonly affected than females.

INCIDENCE OF HYPOGLYCEMIA IN TYPE-2 AND TYPE-1 DIABETES:



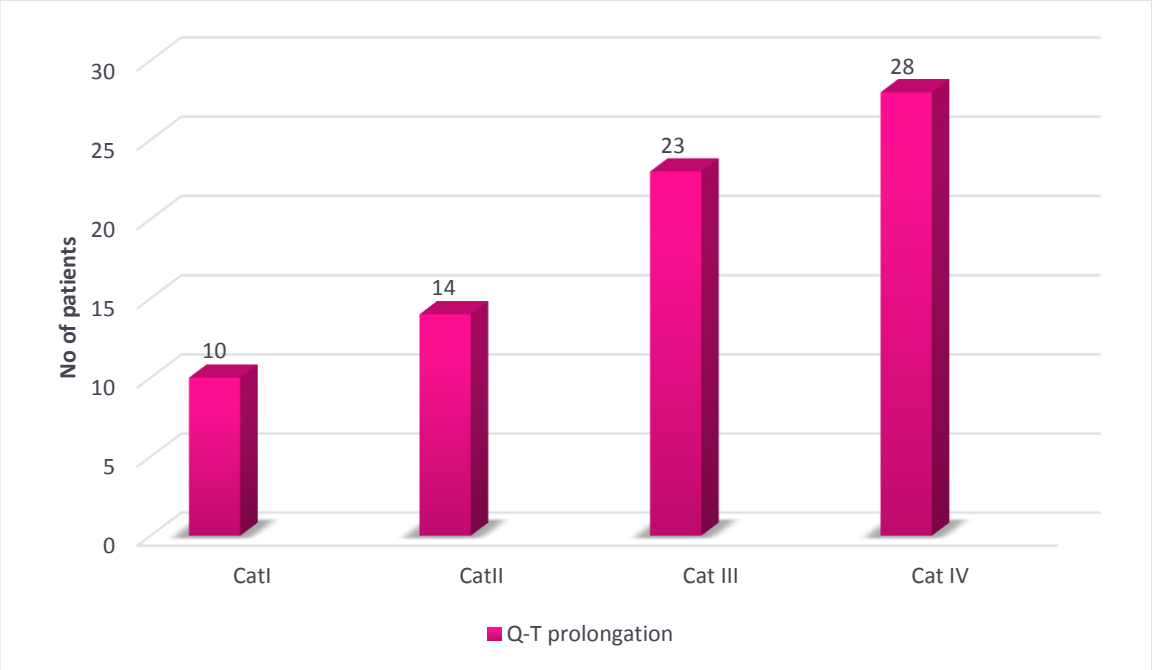
INCIDENCE OF Q-T PROLONGATION IN VARIOUS* CATEGORIES *OF HYPOGLYCEMIA:

Sugar Level	QT(c) Prolongation	Percentage
Cat-I (28)	10	13.33
Cat -II (20)	14	18.67
Cat -III (24)	23	30.67
Cat -IV (28)	28	37.33
Total	75	100
'p' value	**0.048 Significant**	
Chi square value	3.89	

Comments:

24 patients from Cat-1& 2 and 51 patients from Cat-3&4 are developed Q-T prolongation in our study with significant p value of .048.so when hypoglycemia is severe, incidence of Q-T prolongation is also increases due to repolarization abnormalities.

INCIDENCE OF Q-T PROLONGATION IN VARIOUS CATEGORIES OF HYPOGLYCEMIA:



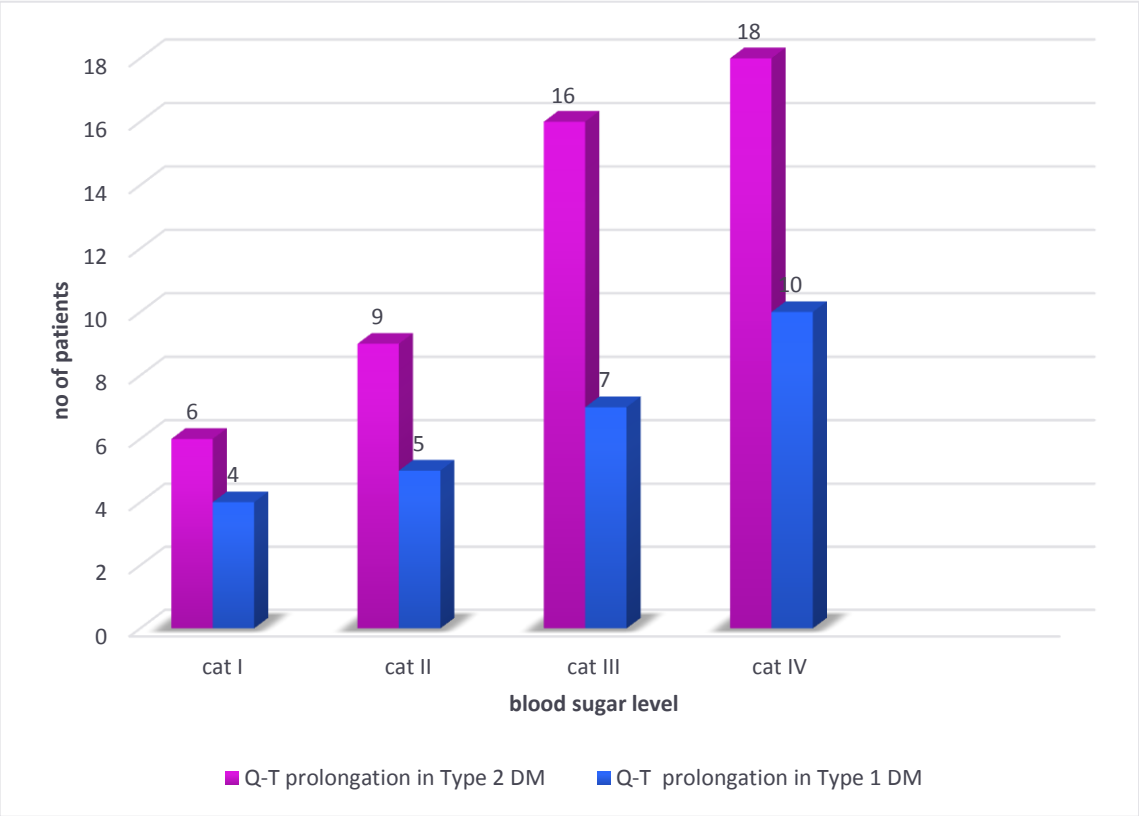
INCIDENCE OF Q-T PROLONGATION IN DIABETIC PATIENTS:

Sugar level mg/dl	Type – I Prolongation (%)	Type - II Prolongation (%)	Total
Cat I	4 (15.38%)	6 (12.24%)	10 (13.33%)
Cat II	5 (19.23%)	9 (18.37%)	14 (18.67%)
Cat III	7 (26.92%)	16 (32.65%)	23 (30.67%)
Cat IV	10 (38.46%)	18 (36.73%)	28 (37.33%)
Total	26	49	75

Comments:

In our study 49 patients in type 2 DM, 26 patients in type 1 DM developed Q-T prolongation. Type 2DM is more common than type 1 DM in our country. Incidence of Q-T prolongation are more with insulin treatment.

INCIDENCE OF Q-T PROLONGATION IN DIABETIC PATIENTS:



MEAN Q-T INTERVAL IN VARIOUS CATEGORES:

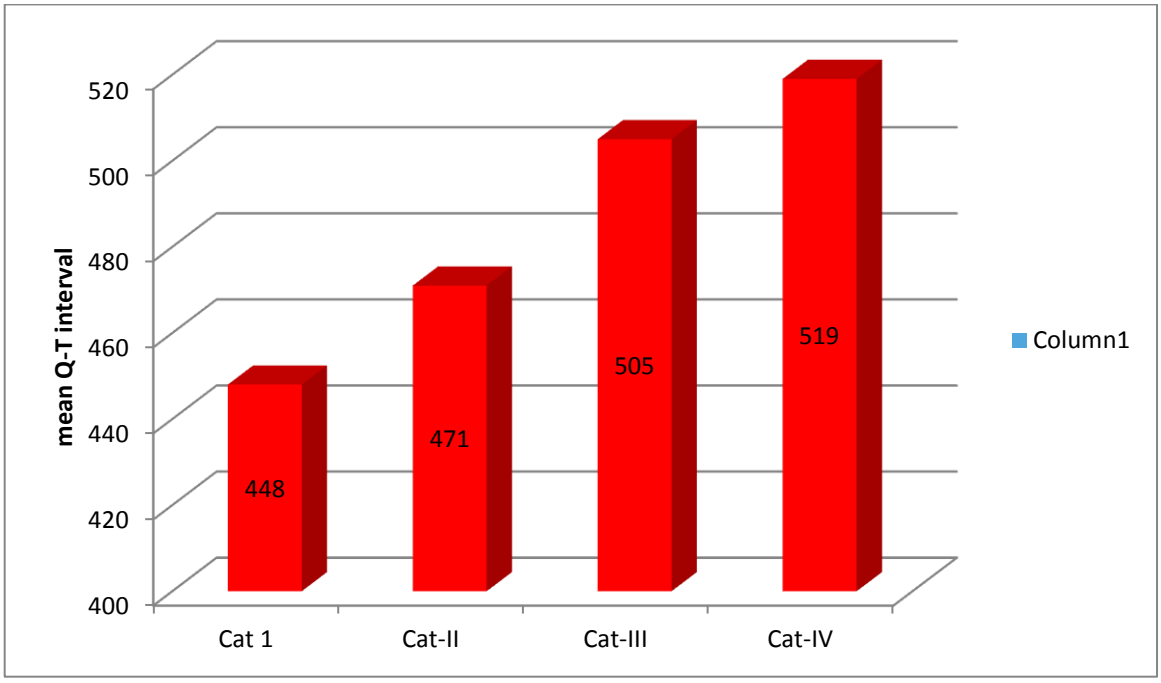
Sugar mg/dl	Mean Q-T interval (ms)
Cat- I	448.21
Cat- II	471.65
Cat-III	505.08
Cat- IV	519.1
P VALUE –0.001	

Comments:

Q-T interval prolongation is depends on the severity of hypoglycemia. In our study 448 ms was a mean Q-T interval in stage 1. As the stage advances Q-T prolongation also increases. Mean Q-T interval of stage 4 was 519 ms.

P value-0.001

MEAN Q-T INTERVAL IN VARIOUS STAGES:

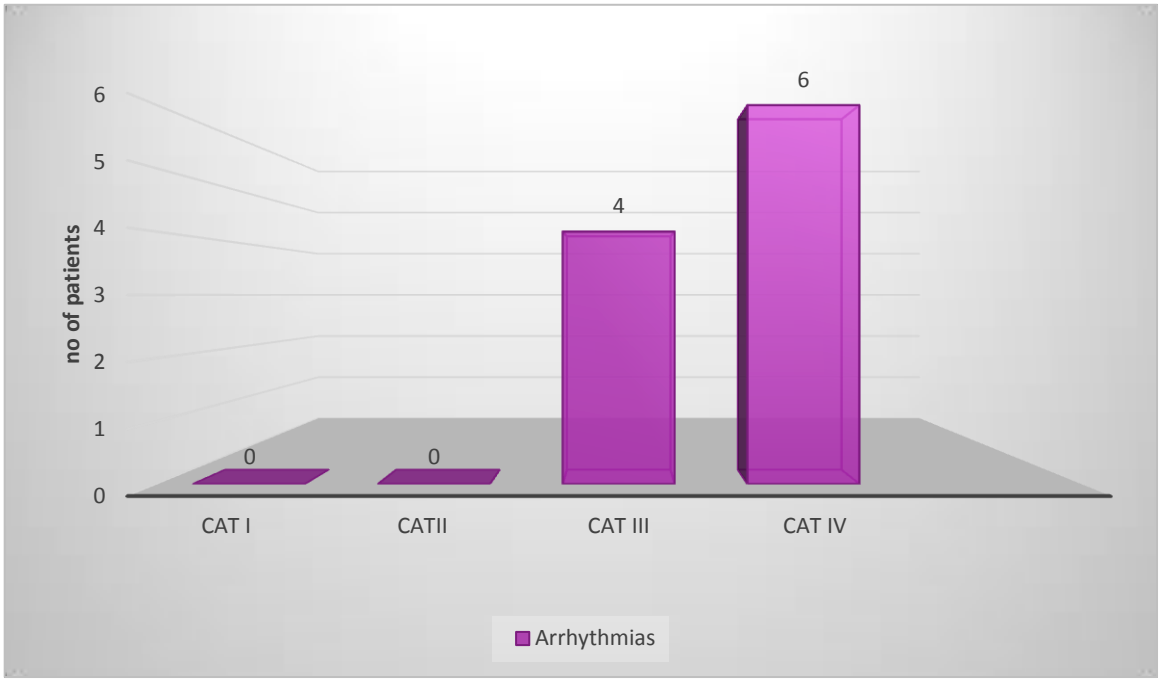


INCIDENCE OF ARRHYTHMIAS IN VARIOUS CATEGORIES OF HYPOGLYCEMIA:

Sugar Level	No of patients with Arrhythmias	Percentage
Cat-I (28)	0	
Cat-II (20)	0	
Cat-III (24)	4	40
Cat-IV (28)	6	60
Total	10	100
'p' value	**0.010** **Significant**	
Chi square value	6.67	

Comments: Hypoglycemia causes repolarization abnormality there by increasing the interval of Q-T. This causes arrhythmias and SCD. In our study 4 patients in Category -III 6 patients in Category- IV developed arrhythmias with statistically significant P value of 0.010. Chi square value-6.67

INCIDENCE OF ARRHYTHMIAS IN VARIOUS STAGES OF HYPOGLYCEMIA:



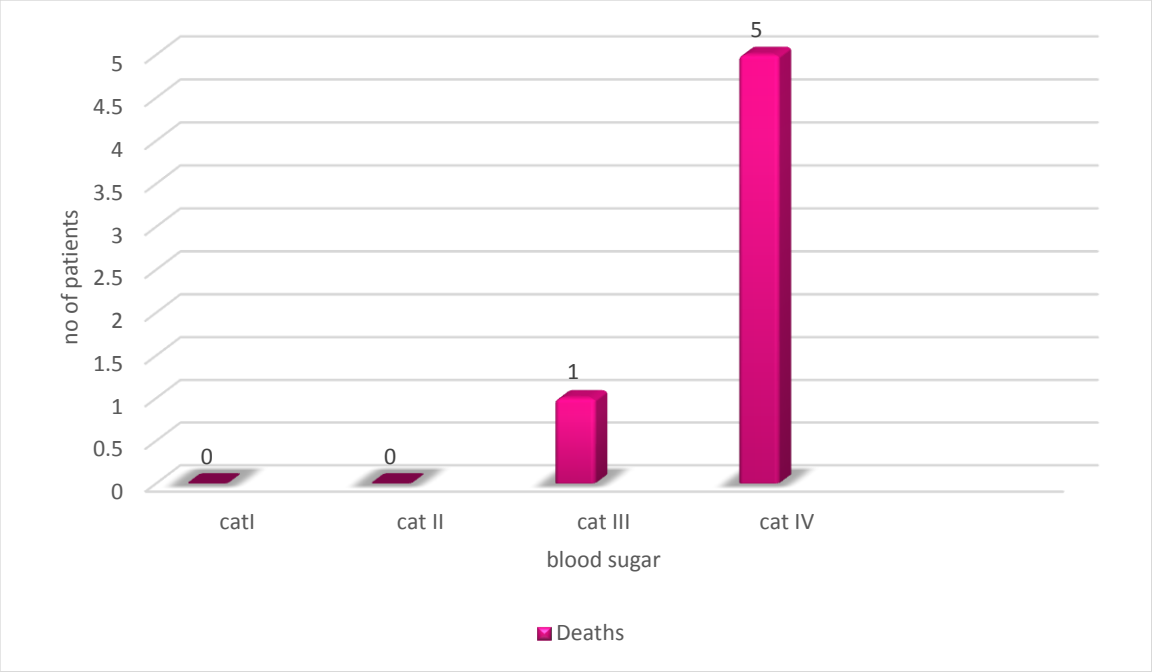
INCIDENCE OF DEATHS IN VARIOUS CATEGORIES OF HYPOGLYCEMIA:

Sugar Level	No of Deaths	Percentage%
Cat-I (28)	0	
Cat-II (20)	0	
Cat-III (24)	1	16.66
Cat-IV (28)	5	83.33
Total	6	100
'p' value	**0.047** **Significant**	

Comments:

Q-T interval is prolonged in severe in hypoglycemia. This prolonged Q-T interval causes arrhythmias and death. In our study 5 patients were died due to arrhythmias in Category -IV and 1 patient died in Category-III. There were no deaths observed in Category I&II with statistically significant P value of 0.047.

INCIDENCE OF DEATHS IN VARIOUS CATEGORIES OF HYPOGLYCEMIA:



INCIDENCE OF Q-T PROLONGATION IN VARIOUS DURATION OF DM:

Duration of Diabetes	Number of patients with Q-T prolongation	Percentage
5 – 10 years (10)	3	4.00
11 – 20 years (30)	14	18.67
21 – 30 years (60)	58	77.33
Total	75	100

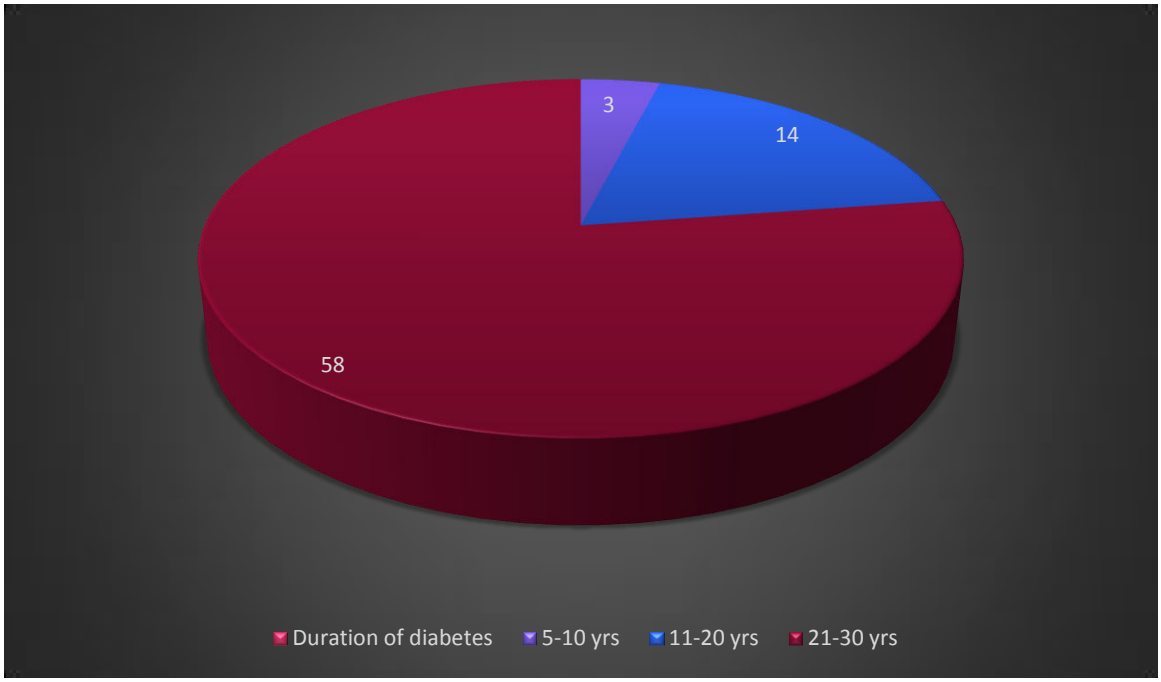
P VALUE --<0.0001 SIGNIFICAN

CHISQUARE –47.2

Comments:

Q-T interval increases when the duration of diabetes increases.in our study 58 patients have 21-30 years of diabetes.14 patients have 11-20 years of diabetes. Only 3 patients have 5-10 years of diabetes.

INCIDENCE OF Q-T PROLONGATION IN VARIOUS DURATION OF DM:



DISCUSSION

Hypoglycemia is one the common complication of DM patients with insulin therapy. Hypoglycemia causes QT prolongation, there by inducing arrhythmias and sudden cardiac death. Incidence of hypoglycemia induced SCD in Indian population is around 1-2%. Repolarization abnormalities during hypoglycemia are the most common cause of arrhythmias among diabetic patients (1). Ventricular tachycardia and fibrillation, atrial fibrillations are the common arrhythmias associated with hypoglycemia (3). In our study hypoglycemia is more in Type 2 DM than Type-1. Prolongation of Q-T c is also more in type-2 DM. Type-2 DM patients have additional risk factors like smoking, alcohol intake, systemic hypertension, obesity, that also responsible for sudden cardiac death in type-2 DM(4). In our study male having higher incidence of hypoglycemia compared to females.

Among diabetes, type-1 DM patients have significantly increased in the frequency of hypoglycemic episodes compared to type-2. Because Type-1 DM patients are dependent on insulin. Though Type-2 patients initially responding to oral hypoglycemic agents, later they require insulin or become insulin dependent, due to progression of disease. Around 50% of beta cells will be lost at the time of diagnosing Type-2 DM (11).

As the age advances with uncontrolled DM, Patients will require insulin for their survival (16). Moreover duration of diabetes is also associated with prolongation of Q-T interval and sudden cardiac death (19).

Glucose level:

- In our study very low glucose level patients have higher incidence of Q-T prolongation. It is due to repolarization abnormalities more in severe hypoglycemia that precipitates arrhythmias.

Sex:

In our study 59 of males, 4 females developed hypoglycemia. 15 males, 13 females had hypoglycemia below 30. Mortality is more below 50 mg/dl.

Type of Diabetes mellitus:

In our study, 71 Type-2, and 29 Type-1 patients had hypoglycemia. 20 patients of Type-2, 8 patients of Type-1 had severe hypoglycemia (<30).

Q-T prolongation:

75 developed hypoglycemia in our study. 24 patients are falling between the blood sugar levels of 40-60 mg/dl. 51 patients developed hypoglycemia below the level of 40 mg/dl. 49 patients are Type-2 and 26

patients are Type –1. Incidence of Q-T prolongation is more below 40mg/dl with statistically significant (p.048)

Arrhythmias:

In our study 10 patients developed Arrhythmias. There is no Arrhythmia between the levels of 40-60 mg/dl. 4 patients between the level of 40-80 and 6 patients below the level of 30 mg/dl developed Arrhythmias with statistically significant ($p<0.016$) chi square value-6.67.

DEATH:

- ⇨ In our study one patient died due to Arrhythmia in blood sugar range of 40-30 mg/dl.
- ⇨ 5 patients died, below the blood sugar level of 30 mg/dl with statistically significant $p<0.047$.

Duration of diabetes:

In our study, as the duration of Diabetes increase. Q-T prolongation also increase with statistically significant ($p<0.001$).Chi square => 47.25.

58 patients with 21-30 yrs of duration of diabetes, 14 patients with 11-20 yrs of duration of diabetes, 3 patients with 5-10 yrs of duration of diabetes developed QT prolongation.

CONCLUSION

From our study we conclude, that

1) Incidence of QTc prolongation is more with severe hypoglycemia.

2) QTc interval more than 500millisecond causes Arrhythmia, thereby causing sudden cardiac death.

3) Repolarization abnormality is the most common cause of arrhythmia in severe hypoglycemia (1).

4) Deaths due to severe hypoglycemia are most common in type 2 Diabetes Mellitus patients.

5) Duration of diabetes mellitus is also a risk factor for developing arrhythmia and sudden cardiac death (19)

LIMITATION OF THE STUDY:

This study has its own limitation. The number of patients in this study is small. Hence generalization of results of the study have to be made with caution.

The study population involved patients seeking medical care in our hospital which is a tertiary care center and hence they may not represent the general population

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PROFORMA

Name: Age/Sex: Occupation:

Presenting complaints:

H/o palpitation, H/o sweating, H/o giddiness, H/o chest pain, H/o tremor, H/o confusion, H/O seizure, H/o headache,

Past History:

H/o DM, HT, CKD, CVD, DRUG INTAKE, CAD.

Clinical Examination:

General Examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy, hydration status

Vitals: PR, BP, RR, SpO2.

Systemic examination: CVS: RS: ABDOMEN: CNS:

Laboratory investigations:

RBS (Venous blood sample for glucose analysis)

Sr. Electrolytes and Sr.Calcium

ECG

Echocardiogram

ABBREVIATIONS

DM	Diabetes Mellitus
ADA	American Diabetes Association
MODY	Maturity Diabetes Onset of Young
GAD	Glutamic Acid Decarboxylase
C-RP	C - reactive protein
MRDM	Malnutrition Related Diabetes Mellitus
FCPD	Fibro Calculus Pancreatic Diabetes
PDDM	Protein deficient diabetes mellitus
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
DKA	Diabetic keto Acidosis
OGTT	Oral Glucose Tolerance Test
TNF	Tumor Necrosis Factor
VLDL	Very Low DensityLipo Protein
LDL	Low DensityLipo Protein
HDL	High Density Lipo Protein
LPL	Lipo Protein Lipase
AGE	Advanced Glycosylated End Products
PUFA	Poly Unsaturated Fatty Acids
MUFA	Mono Unsaturated Fatty Acids
VSMC	Vascular Smooth Muscle Cells

					MASTER CHART						
s.no	name	age	sex	type 1 DM	type 2 DM	duration of DM in years	QTC prolongation	arrythhmias	DEATH	stage	QT interval(ms)
1	Rengasamy	33	M	+	-	10				I	430
2	Anthony samy	36	M	+	-	10				I	432
3	Palpandi	39	M	+	-	5				I	432
4	kuppammal	30	F	+	-	5	p			I	480
5	Pitchai	31	M	+	-	5				I	440
6	kalimuthu	38	M	+	-	10	p			I	465
7	irulayee	36	F	+	-	10				I	455
8	Yesudoss	39	M	+	-	8				I	440
9	karupayee	40	F	+	-	10				I	450
10	cristopher	40	M	+	-	10				I	432
11	shajahan	39	M	+	-	11				I	432
12	ajith	31	M	+	-	13	p			I	465
13	balusamy	30	M	+	-	15				I	440
14	arun	33	M	+	-	18	p			I	470
15	muthusamy	34	M	+	-	18	p			I	472
16	kuppan	41	M	+	-	20				I	428
17	sadaiyan	46	M	+	-	20	p			I	476
18	maruthupandi	47	M	+	-	20	p			I	465

19	periyakaruppan	49	M	+	-	20				I	420
20	adiakavalam	41	M	+	-	19	p			I	468
21	yekalaivan	49	M	+	-	15	p			I	462
22	gopalakrishnan	44	M	+	-	15	p			I	460
23	karupandi	46	M		-	10				I	420
24	isaikitru	49	M	+	-	14	p			I	464
25	shankar	50	M		+	14	p			I	468
26	marimuthu	42	M		+	13				I	430
27	kavirajam	43	M	-	+	18				I	430
28	sangarappan	45	M	-	+	18				I	424
29	sherif	45	M	-	+	19	p			II	481
30	chinnasamy	44	M	-	+	19				II	426
31	andisamy	76	M	-	+	20	p			II	485
32	jegdish	60	M	-	+	20	p			IV	426
33	gurusamy	60	M	-	+	28	p			IV	426
34	syed	55	M	-	+	30	p			II	486
35	vadivu	54	M	-	+	20	P			II	490
36	mani	53	M	-	+	20	P			IV	424
37	rahman	54	M	-	+	28	p			II	496
38	ilangovan	56	M	-	+	20	P			II	482
39	chinnu	59	M	-	+	28	p			III	506

40	ravindran	60	M	+	-	28	p			III	505
41	azar ali	51	M	+	-	28	p	p	p	III	520
42	kasi	55	M	+	-	28	p	p	p	IV	550
43	pasupathi	54	M	+	-	28	p	p	p	IV	548
44	thavasi	55	M	+	-	24	p			III	510
45	sankarapandi	59	M	+	-	24	p			III	512
46	guru	60	M	+	-	22				II	420
47	muthu	52	M	-	+	21				II	426
48	ramaiah	54	M	-	+	21	p			II	481
49	rajesh	55	M	-	+	21	P			II	482
50	periyasamy	56	M	-	+	28	p			III	510
51	murugan	55	M	-	+	24				III	504
52	revathi	56	F	-	+	21				II	460
53	rajathi	59	F	-	+	28	p	p		IV	524
54	aparna	52	F	+	-	21				III	458
55	akshaya	55	F	-	+	17	p			II	460
56	senthamarai kannan	56	M	-	+	18	p			II	486
57	anusuya	58	F	-	+	20	p			II	500
58	anitha	58	F	-	+	11				II	454
59	sindhuja	59	F	-	+	18				II	450
60	sudha	60	F	-	+	22	p			II	496

61	suganya	54	F	-	+	22	p			III	512
62	saranya	55	F	+	-	21	p			III	510
63	adhira	54	F	+	-	23	p			III	508
64	Karthiga	59	F	+	-	24	p			III	510
65	kamatchi	60	F	-	+	24	p			III	505
66	kavitha	60	F	-	+	21	p			II	490
67	karanya	55	F	-	+	22	p			III	510
68	sumalatha	53	F	-	+	23				III	452
69	maheshwari	52	F	+	-	21	P			III	520
70	madhavi	51	F	+	-	24	p			II	482
71	raja	52	M	+	-	21	p			III	518
72	ramu	55	M	+	-	21	P			III	510
73	seenivasan	54	M	+	-	25	P			III	508
74	prem	70	M	+	-	30	p	p	p	IV	545
75	karthick	69	M	+	-	28	p	p	p	IV	544
76	israth	61	M	+	-	25	P			III	510

77	vijayaraja	65	M	+	-	21	p			III	508
78	chinnamariappan	64	M	+	-	24	p			III	504
79	shanmuga sundaram	63	M	+	-	25	p			III	510
80	naveen	62	M	+	-	21	p			III	502
81	sunitha	61	F	+	-	25	p			IV	524
82	leelavathy	69	F	+	-	22	p			IV	526
83	meena	68	F	+	-	21	p			IV	526
84	anu	67	F	+	-	24	p			IV	526
85	teenu	66	F	+	-	25	p			IV	524
86	manimekalai	65	F	+	-	28	p			IV	528
87	muthumari	70	F	+	-	30	p			IV	526
88	thamarai	70	F	+	-	30	p			IV	524
89	devi	65	F	+	-	28	p			IV	524
90	geetha	64	F	+	-	25	p			IV	526
91	ramya	63	F	+	-	25	p			IV	524
92	aarthi	65	F		-	28	p	p		IV	540

				+							
93	abinaya	64	F	-	+	28	p	p		IV	542
94	akalya	65	F	-	+	21	p			IV	522
95	kupammal	62	F	-	+	23	p			IV	524
96	ambal	61	F	0	+	24	P			IV	524
97	amsavalli	61	F	-	+	25	p			IV	526
98	revathi	70	F	-	+	21	P			IV	524
99	rajathi	62	F	-	+	28	p	p		IV	528
100	premalatha	61	F	-	+	30	p	p	p	IV	540

Ref. No. 68/E4/2/2014

Govt. Rajaji Hospital,
Madurai.20. Dated: 02.2014

Institutional Review Board / Independent Ethics Committee.
Captian. Dr. B. Santhakumar, M.D., (F.M.,)
Dean, Madurai Medical College &
Govt Rajaji Hospital, Madurai 625020. **Convenor**

Sub: Establishment-Govt. Rajaji Hospital, Madurai-20-
Ethics committee-Meeting Minutes- for January 2014
Approved list -regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held on 20.1.2014, Monday at 10.00 am to 12.00.noon at the Anaesthesia Seminar Hall, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

1.Dr. V. Nagarajan, M.D., D.M (Neuro) Ph: 0452-2629629 Cell.No 9843052029	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2. Dr.Mohan Prasad , M.S M.Ch Cell.No.9843050822 (Oncology)	Professor & H.O.D of Surgical Oncology(Retired) D.No.72, West Avani Moola Street, Madurai -1	Member Secretary
3. Dr. Parameswari M.D (Pharmacology) Cell.No.9994026056	Director of Pharmacology Madurai Medical College	Member
4. Dr.S. Vadivel Murugan, MD., (Gen.Medicine) Cell.No 9566543048	Professor of Medicine Madurai Medical College	Member
5. Dr.S. Meenakshi Sundaram, MS (Gen.Surgery) Cell.No 9842138031	Professor & H.O.D of Surgery Madurai Medical College	Member
6. Mrs. Mercy Immaculate Rubalatha, M.A., Med., Cell. No. 9367792650	50/5, Corporation Officer's quarters, Gandhi Museum Road, Thamukam, Madurai-20	Member
7. Thiru.Pala. Ramasamy , BA.,B.L., Cell.No 9842165127	Advocate, D.No.72.Palam Station Road, Sellur, Madurai -2	Member
8. Thiru. P.K.M. Chelliah ,B.A Cell.No 9894349599	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20	Member

The following Project was approved by the committee

..2..

Name of P.G.	Course	Name of the Project	Remarks
Dr.K. Ramkumar	PG in M.D., (General Medicine) Madurai Medical College and Government Rajaji Hospital, Madurai.	Assessment of corrected Q-T interval during hypoglycemic episodes in diabetic patients.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it Confidentially.

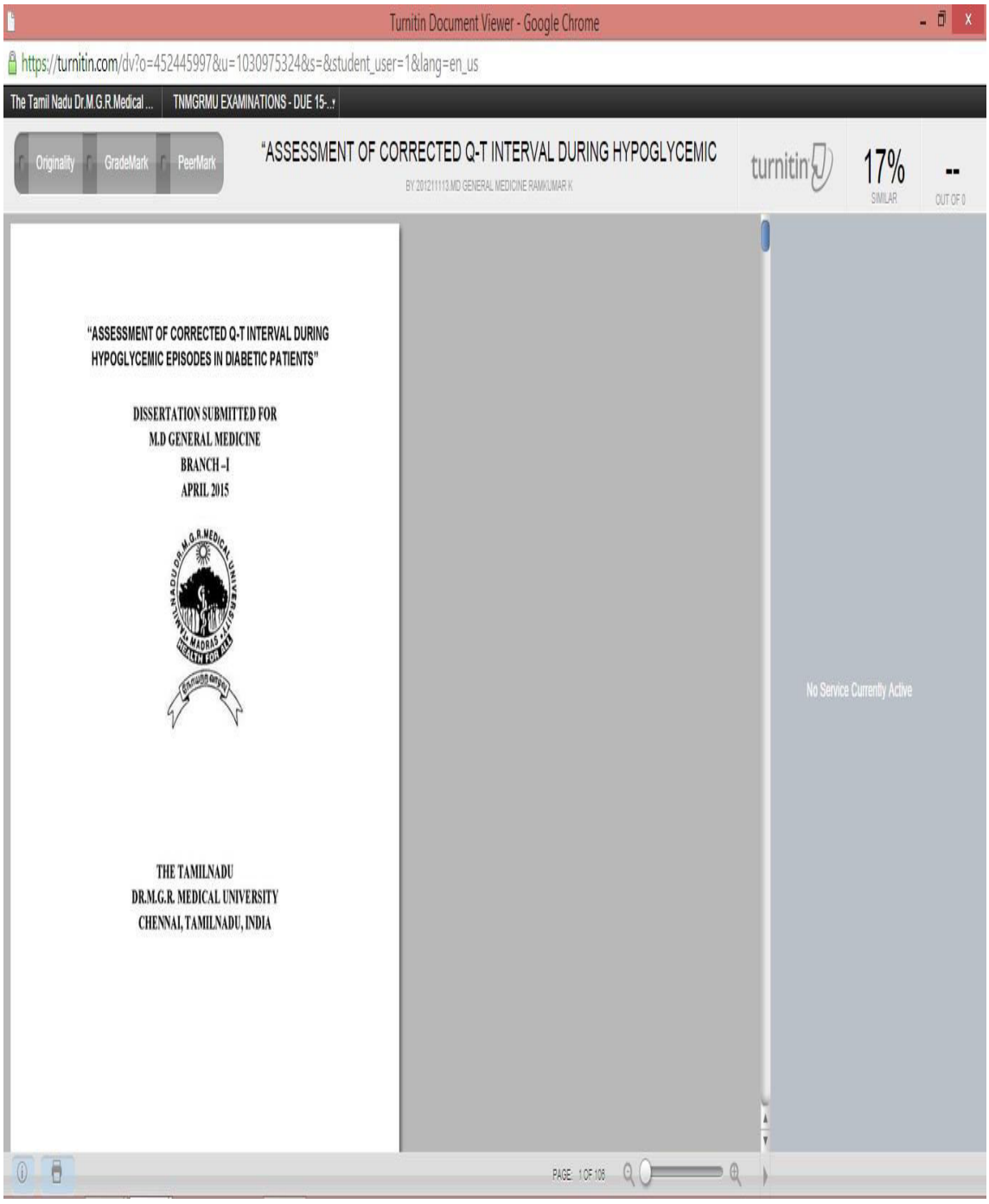
1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary **Chairman**
Ethical Committee

26.2.14
DEAN/Convenor
Govt. Rajaji Hospital,
Madurai- 20.

6/2/14

To
The above Applicant
-thro. Head of the Department concerned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M.D GENERAL MEDICINE
BRANCH –I
APRIL 2015
THE TAMILNADU
DR.M.G.R. MEDICAL UNIVERSITY
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"ASSESSMENT OF CORRECTED Q-T INTERVAL DURING HYPOGLYCEMIC EPISODES IN DIABETIC PATIENTS"

DISSERTATION SUBMITTED FOR M.D GENERAL MEDICINE BRANCH - I APRIL 2015

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY CHENNAI, TAMILNADU, INDIA